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BONE MARROW IN AGRANULOCYTOSIS (PERNICIOUS LEUKOPENIA)

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INTRODUCTION

In the first cases of agranulocytosis which were described by Werner Schultz,[1] the complete absence of granulated cells from the bone marrow of the ribs and femur was the outstanding anatomic feature. The bone marrow was fatty with small islands of lymphoid cells among which a few myeloblasts could be distinguished. Many of the subsequent investigators were able to confirm this statement, stressing the integrity or hyperplasia of the erythropoietic tissue and megakaryocytes in striking contrast to the complete aplasia of the granulocytes (Isaacs,[2] Jackson,[3] Koch,[4] Licht and Hartmann,[5] Oppikofer,[6] Petri,[7] Richards,[8] Schaefer,[9] Uffenorde[10] and others). Several authors observed severe alterative changes of the myeloblasts and myelocytes. Thus, Oppikofer reported that the bone marrow in his cases contained numerous myeloblasts which were either degenerated or necrotic. Rotter[11] described cells with a deeply basophilic and vacuolated cytoplasm and with large pale nuclei containing several nucleoli. He identified the cells which did not give the oxydase reaction with degenerated myeloblasts and myelocytes. Similar cells were found by Koch, and Hueber[12] mentioned myelocytes with vacuoles in the cytoplasm. Rose and Houser[13] observed cells with indistinct, ragged outlines and with hyaline droplets in the cytoplasm in the hyperplastic bone marrow in a typical case of agranuo-

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1. Schultz, Werner: Deutsche med. Wchnschr. **48**:1494, 1922.
2. Isaacs, R.: Am. J. Path. **12**:142, 1931.
3. Jackson, H.: Arch. Path. **4**:324, 1927.
4. Koch, W.: Verhandl. d. deutsch. path. Gesellsch. **25**:53, 1930.
5. Licht, H., and Hartmann, E.: Deutsche med. Wchnschr. **51**:1518, 1925.
6. Oppikofer, E.: Beitr. z. path. Anat. u. z. allg. Path. **85**:165, 1930.
7. Petri, E.: Deutsche med. Wchnschr. **50**:1017, 1924.
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9. Schaefer, R.: Deutsches Arch. f. klin. Med. **151**:191, 1926.
10. Uffenorde, H.: Virchows Arch. f. path. Anat. **287**:555, 1932.
11. Rotter, W.: Virchows Arch. f. path. Anat. **258**:17, 1925.
12. Hueber, W.: Frankfurt. Ztschr. f. Path. **40**:312, 1930.
13. Rose, E., and Houser, K. M.: Arch. Int. Med. **43**:533, 1929.

cytosis. The nuclei of these cells were either pale and ballooned or pyknotic, and some of the cells were completely transformed into a hyaline mass. In one of the cases described by van den Wielen [14] the bone marrow contained many cells the size of myelocytes, with small pyknotic nuclei and without granulation. Uffenorde spoke of large cells with a pale cytoplasm and various forms of nuclear degeneration. Hartwich [15] and Petri had difficulty in classifying the atypical cell forms which they encountered in the bone marrow.

According to Fried and Dameshek,[16] there is often a widespread necrosis of the leukopoietic tissue in the severe forms of agranulocytosis, a statement which was also made by Naegeli [17] in the recent edition of his textbook. In two of his four cases of agranulocytosis, Koch found foci of necrosis in the bone marrow, liver and spleen.

In the bone marrow deprived of its granulated elements small lymphocytes are often present in great number (Koch, Petri, Uffenorde, Zikowsky,[18] Zadek,[19] Rotter, Hueber, Komerell [20] and others), and the small lymph follicles which are common in normal bone marrow may be conspicuous (Hallermann [21]). Koch, Baltzer [22] and Zikowsky described plasma cells, and Rotter, Hallermann, Koch and W. Schultz and Jacobowitz [23] reported on hyperplasia of the reticulohistiocytic elements which may show erythrophagocytosis and iron pigmentation.

The cases of agranulocytosis in which the bone marrow reveals severe alterative changes or complete exhaustion of the granulopoietic tissue are in contrast to those cases in which the bone marrow is found to be normal or hyperplastic without apparent injury to the granulopoietic tissue. In 1925, David [24] described a case of marked neutropenia in which the bone marrow contained many myeloblasts, myelocytes and neutrophilic leukocytes. He suggested a disturbance in the emigration of the mature leukocytes from the bone marrow. His case, however, is not typical since there was a severe anemia associated with the agranulocytosis. Reichenbach's [25] patient showed at autopsy a fatty bone marrow with cellular areas which were chiefly composed of promyelocytes. These promyelocytes were well preserved, and only a few

14. van den Wielen, K.: Frankfurt. Ztschr. f. Path. **44**:34, 1932.
15. Hartwich, A.: Ergebn. d. inn. Med. u. Kinderh. **41**:202, 1931.
16. Fried, B. M., and Dameshek, W.: Arch. Int. Med. **49**:94, 1932.
17. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 5, Berlin, Julius Springer, 1931.
18. Zikowsky, J.: Wien. klin. Wchnschr. **44**:203, 226 and 259, 1931.
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20. Komerell, B.: Med. Klin. **25**:1816, 1929.
21. Hallermann, W.: Folia haemat. **42**:1, 1930.
22. Baltzer, H.: Virchows Arch. f. path. Anat. **262**:681, 1926.
23. Schultz, W., and Jacobowitz: Med. Klin. **21**:1642, 1925.
24. David, W.: Med. Klin. **21**:1229, 1925.
25. Reichenbach, G.: Folia haemat. **45**:376, 1931.

of them contained vacuoles. Reichenbach agreed with the explanation offered by David. He failed to report on the blood changes during life. In one of the cases of Dameshek and Ingall [26] in which a sternal biopsy was done during life the bone marrow showed nothing abnormal. Zikowsky, who had at his disposal numerous carefully studied cases of agranulocytosis, observed considerable differences in the cellular picture of the bone marrow. He believes that in the early stages of agranulocytosis there is a blockade of the bone marrow which prevents the mature granulocytes from entering the blood stream. If this blockade persists over a longer period of time, the parental cells of the granulocytes degenerate and break down. Fitz-Hugh and Krumbhaar [27] gave a detailed histologic account of the hyperplastic bone marrow in a case of agranulocytosis. Although mature neutrophilic and eosinophilic leukocytes were absent, there was an abnormal number of young myelocytes with pale nuclei and many neutrophilic granules. These young myelocytes formed 20 per cent of the bone marrow cells. Fitz-Hugh and Krumbhaar came to the conclusion that at least occasionally death may occur in an uncomplicated agranulocytic angina with a profound peripheral leukopenia while the leukopoietic centers are well supplied with parental cells. They consider it likely that a maturation factor is at work either arresting the development of the white cells or producing degenerative changes in them before sufficient development has taken place for the migration into the blood stream. In a subsequent paper with Comroe, Fitz-Hugh [28] again put the maturation arrest before the primary aplasia of the granulopoietic tissue of the bone marrow. The presence of apparently normal myeloblasts and myelocytes in the bone marrow in some of the cases of agranulocytosis was also stressed by Naegeli [17] and Leuchtenberger.[29]

The brief discussion of the literature on the condition of the bone marrow in agranulocytosis discloses a great variety of observations which, at the first glance, is difficult to reconcile with the conception that agranulocytosis is a definite disease entity. In compiling the summary of the literature, many cases reported as agranulocytosis had to be eliminated. In some of the reports the description of the bone marrow is so incomplete that no conclusion can be drawn as to its actual appearance. A considerable number of cases do not belong to the group showing typical agranulocytosis but are more related to cases of aplastic anemia (panmyelophthisis) or aleukia hemorrhagica (Frank).

In a series of cases of agranulocytosis I have observed peculiar changes in the myelocytes which, according to my knowledge, have not

26. Dameshek, W., and Ingall, M.: Am. J. M. Sc. **181**:502, 1931.
27. Fitz-Hugh, T., and Krumbhaar, E. B.: Am. J. M. Sc. **183**:104, 1932.
28. Fitz-Hugh, T., and Comroe, B. J.: Am. J. M. Sc. **185**:552, 1933.
29. Leuchtenberger, R.: Folia haemat. **39**:63, 1929.

yet been reported. In view of the great interest which has been given in recent years to the problem of agranulocytosis, a description of these changes seems to be warranted. They may also help clear the much disputed question whether or not there is an essential difference between so-called idiopathic and symptomatic agranulocytosis. In the majority of the cases bone marrow was taken from the ribs, the vertebrae and the upper third of the diaphysis of the femur. Since the paper deals with fine morphologic changes, stress will be laid chiefly on the bone marrow of the femur. In my experience, even the most careful decalcification interferes somewhat with the Romanowsky stains. Concerning the technic, I refer to my previous publication on the erythropoiesis in leukemia.[30] The optic used consisted of a Zeiss apochromatic oil immersion lens (num. ap. 1.30, f : 1.5 mm.) and a compensation eye piece no. 15.

REPORT OF CASES

So-Called Idiopathic Agranulocytosis.—CASE 1.—A white woman, aged 57, with an illness of three weeks' duration, stated that during the past winter she had rheumatic pains and had suffered from an attack of "flu," during which her temperature rose to 103 F. for seven days. She never recovered completely from this attack. In May, 1932, her throat became very sore, and an abscess developed in the right tonsil. Since her condition did not improve under the care of her doctor, she entered the hospital on May 20, 1932. She appeared very toxic, with a slight icteric tint to the skin and sclerae. The temperature varied between 100.2 and 102 F. Both tonsils were transformed into ulcers that were covered by a foul-smelling necrotic tissue. There was a furuncle over the wrist of the left hand. The urine contained many hyaline and granular casts and single pus cells. Albumin was present (4+). The Wassermann and Kahn reactions were negative. The blood cultures remained sterile for ten days. The blood picture showed: hemoglobin (Dare), 70 per cent; erythrocytes, 4,000,000; white cells, 800; lymphocytes, 70 per cent, and monocytes, 30 per cent. In spite of two blood transfusions, the patient died two days after admission to the hospital.

The pathologic anatomic diagnosis was: severe ulcerative pharyngitis; beginning necrosis of the skin of the left side of the neck with marked edema of the subcutaneous tissue; hemorrhagic serous parotitis of the right side; hyperplasia of the peribiliary lymph nodes; infectious softening of the spleen (weight of the spleen, 385 Gm.); moderate fatty changes of the liver; passive congestion of the kidneys with arteriosclerotic pitting; focal interstitial myocarditis (weight of the heart, 350 Gm.); strawberry gallbladder; ancient supracervical hysterectomy, bilateral salpingectomy and oophorectomy, and slight icterus.

On macroscopic examination the bone marrow of the femur appeared soft and reddish brown, with small light yellow areas. Microscopically, many foci of cells were found which formed 27 per cent of the bone marrow, while the rest consisted of fat tissue. In addition to the cellular foci, there were single small lymph follicles. The capillaries and sinusoids were congested with blood. The reticular cells were not swollen.

The cellular foci were composed of the following elements: myeloblasts, 1.24 per cent; neutrophilic myelocytes, 34.4 per cent. These cells were on the average

30. Jaffé, R. H.: Folia haemat. **49**:51, 1933.

larger than the forms seen in normal bone marrow. Their outlines were often irregular with pseudopodia-like protrusions. The nuclei were oval and showed a distinct membrane and several chromatin granules which were connected by fine threads. The cytoplasm stained a light purple blue with azure II-methylthionine chloride, U.S.P. (methylene blue). The granules were severely changed. Only a few of the cells revealed single intact purple-red granules near the nucleus. In the majority of the cells the granules were swollen, ill defined and transformed into pink specks which seemed to fuse with the cytoplasm (fig. 1). In some of the cells with intact granules mitotic figures were seen. There were 1.80 per cent erythrogonia, 20.39 per cent erythroblasts and 19.85 per cent normoblasts. The segmentation of the nuclei of the normoblasts started before pyknosis had obscured the chromatin structure. The nuclear segments showed, therefore, a coarse chromatin net. There were 0.35 per cent megakaryoblasts and 2.30 per cent megakaryocytes. The majority of the megakaryocytes had lost their granulation, and their nuclei were pyknotic. There were 12.41 per cent lymphocytes and 5.67 per

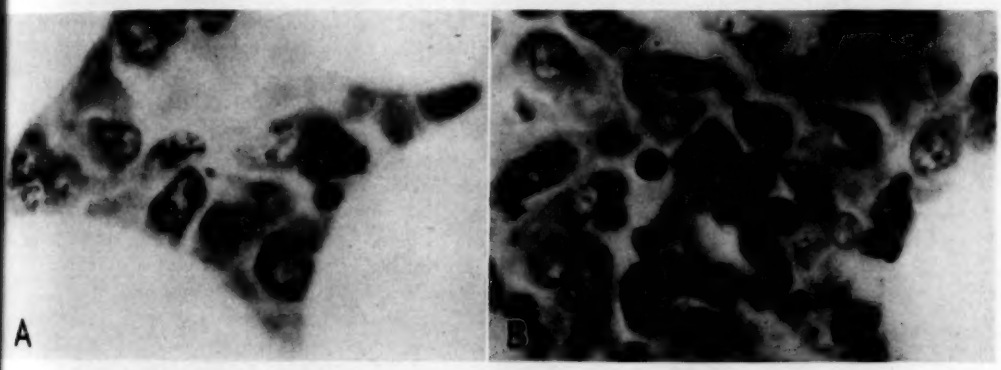

Fig. 1 (case 1).—Bone marrow showing different forms of degeneration of the neutrophilic myelocytes. Note the transformation of the granules into ill-defined specks. In *A*, vacuoles can be seen about some of the granules. The nuclei are still well preserved. In the center of *A* is a mitosis which is not in the focus. In *B*, plasma cells and lymphocytes appear between the myelocytes. Zenker-formaldehyde fixation; Giemsa stain; magnification, × 1,200.

cent plasma cells. Some of the plasma cells were large and contained two nuclei. There were 1.54 per cent monocytoid cells.

Among the histologic changes in the other organs, I mention the absence of oxydase positive cells from the spleen, the pulp of which contained many plasma cells and mobilized histiocytes. After a long search, a single myelocyte with scanty granules was found in a periportal lymph node.

Case 2.—A white woman, aged 27, with an illness of six days' duration, had an attack of tonsillitis on May 14, 1932, from which she recovered. She felt well until June 6, when an abscess at the root of the right lower canine developed which necessitated extraction of this tooth. Because of pain and swelling, the site of extraction was lanced the following day, and the lesion improved. During the night from June 11 to 12 the patient experienced severe, cramplike abdominal pains centering about the umbilicus. A physician diagnosed the condition appendicitis, and an ice bag was applied which relieved the pains. The next evening

she complained of a slight soreness of her throat which, during the next two days, became severe and was accompanied by high fever, dysphagia, insomnia and choking sensations. Although the throat culture did not show any diphtheria bacilli, 10,000 units of diphtheria antitoxin was given subcutaneously. The patient entered the hospital on June 15. On admission the tonsils were found covered by necrotic membranes, the tongue was coated, and the uvula was markedly edematous. Smear from the tonsils revealed many spirochetes and fusiform bacilli. The temperature remained around 103 F. The blood picture showed: hemoglobin, 85 per cent; erythrocytes, 4,500,000; white cells, 150; lymphocytes, 70 per cent; monocytes, 30 per cent; platelets, 250,000. The patient died two days after admission.

The pathologic anatomic diagnosis was: gangrenous tonsillitis, pharyngitis and glossitis; marked edema of the larynx; a recent tracheotomy wound with aspirated blood in the trachea and main bronchi; fatty changes of the liver; infectious softening of the spleen (weight, 160 Gm.), and parenchymatous degeneration of the myocardium and the kidneys.

Macroscopically, the bone marrow of the femur was moderately firm and purple red with single purple-brown and light yellow areas. Microscopically, about 52 per cent of the marrow was cellular, the remaining part being made up of fat tissue.

The cells were composed of 48.8 per cent of large elements with an ample homogenous or finely vacuolated cytoplasm (fig. 2). The outlines of these cells were irregular with pseudopodia-like protrusions. With azure II-methylthionine chloride the cytoplasm stained from light blue to bluish gray with a light pink hue near the nucleus. The nuclei were oval or bean-shaped and contained a sharply defined chromatin structure. Namely, there were large and small granules which were connected by fine threads. The nucleoli were indistinct and appeared pale pink. A few of these cells showed mitotic division of the nucleus. The chromosomes were short and plump and irregularly arranged. After a long search, a single cell was discovered which contained a fine, purple-pink granulation. In addition to the cells described, there were 10.6 per cent plasma cells, some of which were large with two nuclei, 10.6 per cent erythroblasts, 15.2 per cent normbolasts, 2.6 per cent megakaryocytes, 1.2 per cent megakaryoblasts and 11 per cent lymphocytes. Besides the loosely scattered lymphocytes, single small lymph follicles were found. The picture of the bone marrow of the rib was similar except that the cellularity amounted to 74 per cent.

The pulp of the spleen was rich in plasma cells which often formed small colonies with mitotic figures. There were also many free histiocytes, some of which contained red blood cells. The oxidase reaction failed to demonstrate a single granulocyte. The Kupffer cells of the liver were much swollen and often mobilized. The lymph nodes showed marked erythrophagocytosis by the proliferated sinus endothelial cells, and many plasma cells in the cords of the medulla. Underneath the thick necrotic membranes of the pharynx there was an edematous zone with deposits of fibrin. The zone was loosely infiltrated by small round cells and large free histiocytes with an ample vacuolated cytoplasm and small kidney-shaped nuclei. The adventitial cells of the blood vessels were much swollen and proliferated, and their cytoplasm was deeply basophilic.

Case 3.—A white woman, aged 24, with an illness of fourteen days' duration, had two teeth extracted on April 12, 1932. Two days later a constant pain in her jaw developed. She also noticed a tender nodule on the left side of the neck, and her throat felt sore. Swallowing was painful, and she felt hot and chilly at times. She entered the hospital on April 27. Her throat was inflamed,

and the cervical lymph nodes of the left side of the neck were swollen. The temperature ranged from 103 to 105 F. Two days later, the tonsils and tonsillar pillars were found covered by a foul-smelling, dirty gray membrane. Two days prior to her death a profuse diarrhea with severe abdominal pains developed. In spite of various therapeutic measures such as blood transfusions, roentgen therapy to the long bones, fresh bone marrow by mouth and intravenous injections of a solution resulting from the action of iodine on sodium carbonate solution, the patient died on May 7. Blood culture showed a pure growth of Staphylococcus

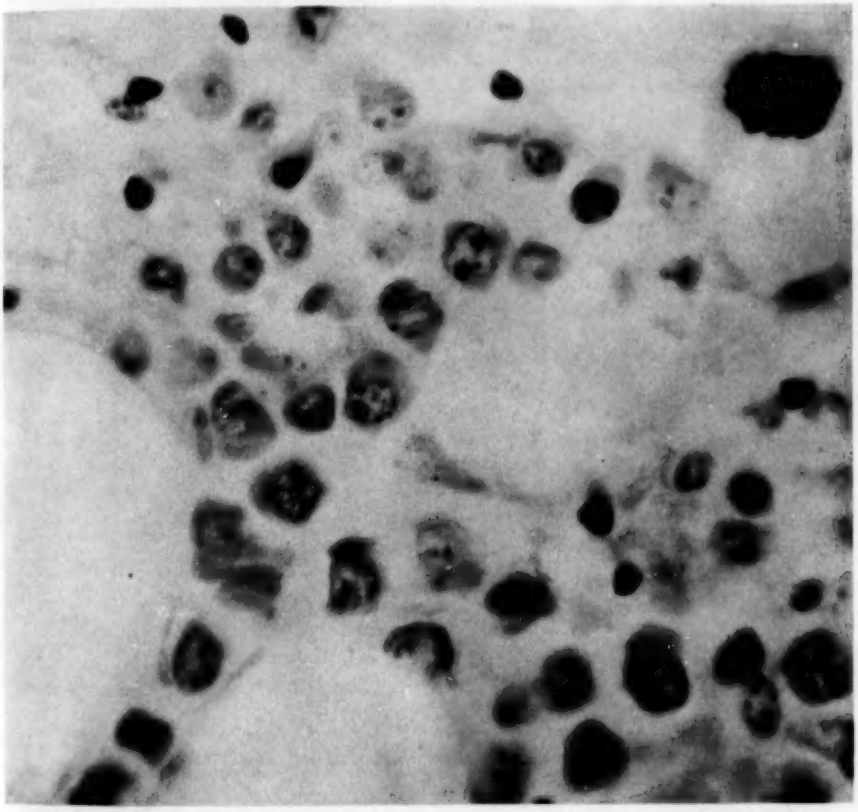

Fig. 2 (case 2).—Bone marrow. The myelocytes have lost their granulation and in the nuclei the chromatin is separated into irregular granules. There are several plasma cells and a degenerated megakaryocyte in the field. Technic and magnification same as in figure 1.

albus. The blood picture showed: hemoglobin, 70 per cent; erythrocytes, 3,249,000; white cells, 800; lymphocytes, 89 per cent; monocytes, 9 per cent; irritation forms, 2 per cent, and platelets, 340,000.

The pathologic anatomic diagnosis was: gangrenous tonsillitis; pseudomembranous esophagitis; gangrenous ulcerative enteritis and colitis; hyperplasia of the cervical, mesenteric and axillary lymph nodes; moderate fatty degeneration of the myocardium, liver and kidneys; hyperplasia of the spleen (weight, 318 Gm.); slight fibroplastic deformity of the mitral valve, and focal myocardial fibrosis.

On gross examination the bone marrow of the femur was soft and reddish brown. Microscopically, 62 per cent of the marrow was made up of dense accumulations of cells. The capillaries were much engorged with blood.

Similar to the bone marrow in the second case, there were numerous large lymphoid cells with a basophilic vacuolated cytoplasm and coarsely granular nuclei. The cells contained no granules and did not give the oxidase reaction. Their percentage amounted to 29. The most striking feature, however, was the great number of megakaryocytes (8.6 per cent mature forms and 2.2 per cent megakaryoblasts). About half of the megakaryocytes were well preserved (fig. 3 A), while the other half showed different stages of degeneration with karyolysis which terminated in complete necrosis (fig. 3 *B*). The megakaryoblasts were intact and often were found in mitotic division with large chromosomes. There were 3.6 per cent erythroblasts, 3.6 per cent normoblasts, 27.2 per cent lymphocytes,

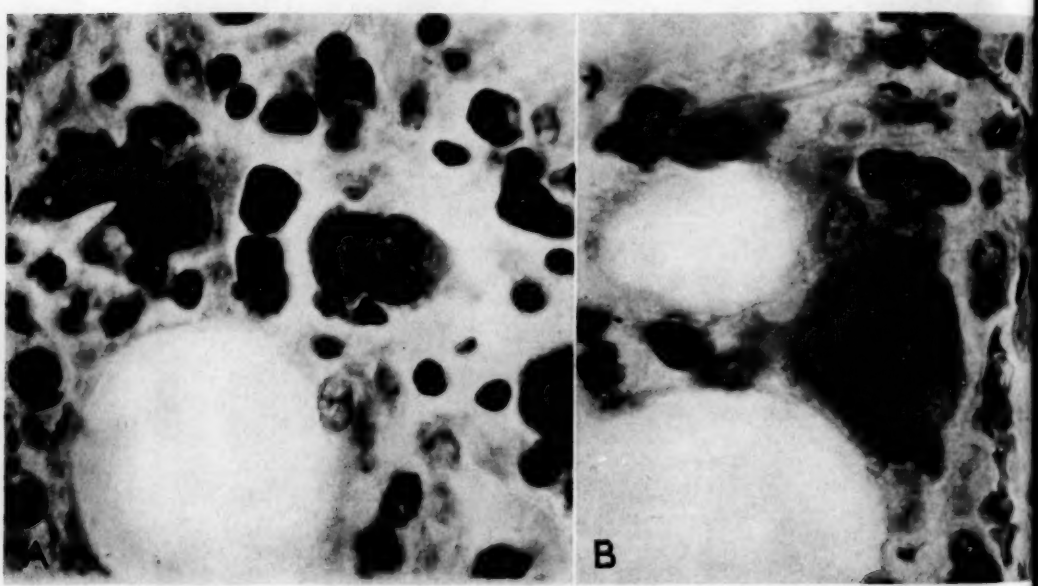

Fig. 3 (case 3).—Bone marrow showing: *A*, well preserved megakaryocytes; *B*, necrotic megakaryocyte. Technic and magnification same as in figure 1.

22.8 per cent plasma cells and 3 per cent free histiocytes. Between these different types of cells a fine net of fibrin could be demonstrated, and there were many recent extravasations of blood. The histologic picture of the bone marrow of the rib was similar except that the megakaryocytes formed 15 per cent of the cells, and nucleated red cells were fewer.

In the spleen a diffuse thickening of the reticulum was found. The endothelial cells of the sinusoids and the reticular cells of the cords of the pulp were swollen, and the pulp contained many plasma cells and a few normoblasts. Not a single granulocyte could be detected. In the lymph nodes, too, the reticulum was thickened, and there was a hyperplasia of the reticulo-endothelial cells. Underneath the necrotic membranes of the esophagus and intestine there was much edema with thrombosis of the blood vessels. The loose connective tissue contained many large, free histiocytes with vacuolated cytoplasm.

CASE 4.—A white woman, aged 43, whose illness was of four weeks' duration, stated that she was well until a month before when her gums became swollen and painful. A week later a sore throat developed which was associated with much cough productive of pus and mucus. The patient had a similar attack in Paris in May, 1929. This time, her condition became progressively worse, and the temperature rose to 102 F. She entered the hospital on Nov. 16, 1929. The right nostril showed an ulceronecrotic lesion. The right tonsil was covered by a thick, adherent dirty gray membrane, and the cervical lymph nodes were slightly swollen. Smears from the right tonsil revealed many diplococci but no spirochetes or fusiform bacilli. The urine contained albumin (3 +) and a few hyaline casts. The blood picture showed: hemoglobin, 75 per cent; erythrocytes, 4,050,000; white cells, 350; lymphocytes, 94 per cent; monocytes, 4 per cent, and neutrophilic leukocytes, 2 per cent. The patient died on November 19.

The pathologic anatomic diagnosis was: gangrenous tonsillitis; ulceration of the skin of the right nostril; slight eccentric hypertrophy of the heart (weight, 330 Gm.); scars in the wall of the left ventricle and a partially organized thrombus about an aberrant tendon cord of the left ventricle; miliary abscesses of the kidney (staphylococci); arteriolosclerosis of the kidneys, liver, spleen and pancreas; recent hemorrhages in the lungs; slight fatty changes of the liver and passive congestion of the spleen (weight, 190 Gm.).

Macroscopically, the marrow of the femur was soft and pale yellow gray. Microscopically, it appeared fatty with scattered islands of cells, some of which were typical lymph follicles. The other islands were composed of the lymphoid cells described in cases 2 and 3 and of erythroblasts and normoblasts. There were a moderate number of well preserved megakaryocytes. A few oxyphilic granulocytes were found after considerable searching. The bone marrow of the vertebral bodies was more cellular than that of the femur. Megakaryocytes were numerous, and there were also many megakaryoblasts. In addition to the cells found in the femur marrow, plasma cells and monocytoid cell forms were present. The bone marrow of the sternum and the ribs resembled the vertebral marrow. In the ribs the plasma cells were numerous, and fibrin was seen between the cells.

The abscesses in the kidney were formed by histiocytes with small fat globules and by lymphocytes. In the sections stained for oxidase few cells with single granules were seen in the abscesses. There was a moderate activation of the Kupffer cells of the liver and of the reticular cells of the spleen and lymph nodes.

CASE 5.—A white woman, aged 52, with an illness of six days' duration, was well until Dec. 30, 1931, when she experienced severe pains in the rectum during and following defecation. The painful defecation was accompanied by the passage of a large amount of bright red blood. The following day she complained of a sore throat which increased so much in severity that she was unable to swallow. At the same time her neck became swollen. She entered the hospital on Jan. 4, 1932. On the soft palate just superior to the right tonsil there was an irregular ulcer about the size of a dime, the floor of which was black. Both sides of the neck were swollen and tender. Her temperature on admission was 101 F. The urine contained albumin (2 +), a trace of bile and a few pus cells and hyaline casts. The blood culture showed hemolytic staphylococci; the throat culture, staphylococci, Micrococcus catarrhalis and Micrococcus tetragenus. The blood picture showed: hemoglobin, 70 per cent; erythrocytes, 3,600,000; white cells, 700; lymphocytes, 84 per cent; monocytes, 16 per cent. The patient died fifteen hours after admission to the hospital.

The pathologic anatomic diagnosis was: gangrenous lesions of the mouth, throat, upper lip, skin of the neck and mucocutaneous junction of the rectum and

at the cardia of the stomach; slight fibroplastic deformity of the mitral valve; dilatation of the left cardiac chamber with sclerosis of the endocardium; fatty changes of the liver and kidneys; fibrosis of the splenic pulp (weight of spleen, 170 Gm.) and slight icterus.

The marrow of the femur was light yellow and fatty. It contained single light brown areas which were located chiefly in the periphery. Microscopic examination revealed fat tissue with much congested capillaries. Some of the capillaries were occluded by fibrin, and fibrin was also found between the cells. Scattered between the fat cells there were small accumulations of lymphocytes and of larger lymphoid round cells with a deeply basophilic cytoplasm and round nuclei the chromatin net of which was coarse. Some of these cells were vacuolated, and the content of the vacuoles assumed a light pink color. There were also a few small groups of orthochromatic normoblasts, a moderate number of plasma cells and of monocytoid elements with bluish-gray cytoplasm and kidney-shaped nuclei, and a few megakaryocytes the nuclei of which either stained diffusely or were broken up into irregular segments. The reticular cells were prominent and contained red blood cells. The adventitial cells of the blood vessels were swollen, and their ample cytoplasm was stained a deep blue.

In the spleen the reticular cells of the pulp were swollen and mobilized, and some of the reticular cells contained red blood cells. The cords harbored a moderate number of plasma cells. The trabeculae were infiltrated by lymphoid round cells which extended to the endothelium of the trabecular veins. The Kupffer cells of the liver and the reticular cells of the lymph nodes were swollen and increased in number. The necrotic lesions in the mouth, throat, neck and rectum were separated from the intact tissue by accumulations of lymphocytes and plasma cells. The capillaries and veins were wide and were often occluded by fibrin or mixed thrombi.

Agranulocytosis Following Antisyphilitic Treatment.—Case 6.—A Negress, aged 38, with an illness of four weeks' duration, began to feel weak and to have pains in both arms and legs, three and a half weeks before entrance to the hospital. She consulted a physician who, after having found that her blood gave strongly positive Wassermann and Kahn reactions, gave her two injections of neoarsphenamine followed by two injections of mercury oxicyanide. She received a third injection of neoarsphenamine and mercury cyanide. At the time of the first injection her temperature was 101.8 F. After the last injection she had a severe reaction and was advised to go to the hospital. On entrance to the hospital she complained of shortness of breath and diarrhea, with stiffness of the legs and inability to walk. She had had four pregnancies and two miscarriages, the last one nine months before. She admitted taking alcohol to excess. Her temperature was 104 F. She had great difficulty in speaking, and an examination of the throat disclosed several large ulcerated areas in the pharynx and at the base of the tongue. Her neck was very tender. Cultures taken from the throat revealed hemolytic streptococci. The blood picture showed: hemoglobin, 70 per cent; erythrocytes, 3,700,000; white cells, 3,500; lymphocytes, 32.8 per cent; monocytes, 67.2 per cent, and blood platelets, 340,000. The patient died six days after admission.

The pathologic anatomic diagnosis was: gangrenous ulcerative glossitis; ulcerative colpitis; severe parenchymatous degeneration of the myocardium and kidneys; fatty changes of the liver; hypostatic pneumonia in both lower pulmonary lobes and recent fibrinous pleuritis over the left lower lobe; fibrinous pericarditis; infectious softening of the spleen (weight of the spleen, 245 Gm.); nodose goiter, and fibrous adhesions about the ileum, sigmoid colon and both ovaries and tubes.

The marrow of the femur was soft, light yellow-gray mottled with pale purple-red. Microscopically, 70 per cent of the marrow was found to be composed of islands of cells which contained the following types of cells: myeloblasts, 1.2 per cent; neutrophilic myelocytes, 54.2 per cent; neutrophilic leukocytes, 6.4 per cent; eosinophilic myelocytes, 3.4 per cent; eosinophilic leukocytes, 1.4 per cent; erythrogonia, 2.4 per cent; erythroblasts, 6.2 per cent; normoblasts, 17.2 per cent; megakaryoblasts, 0.4 per cent; megakaryocytes, 1 per cent; lymphocytes, 0.2 per cent; plasma cells, 6 per cent. While the myeloblasts appeared well preserved, the neutrophilic myelocytes showed severe changes (fig. 4). The granules were swollen and took the stain poorly. Their outlines were irregular and indistinct, and one obtained the impression that the granules would melt away and would mix with the cytoplasm which was finely vacuolated. In the nuclei the chromatin was separated in the form of large and irregular clumps. Some of the cells were free from granules; their nuclei were either fairly well preserved or pyknotic. There was an occasional mitotic figure in a cell the granules of which were relatively well defined. The mature neutrophilic leukocytes revealed an excessive lobulation of the nuclei and changes of the granules similar to those seen in the myelocytes. In the oxyphilic granulocytes the alteration of the granules was less

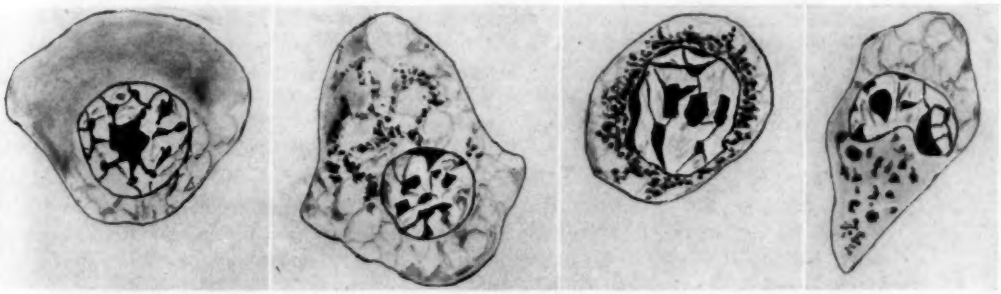

Fig. 4 (case 6).—Ink sketch of the bone marrow showing the gradual disappearance of the granules and the vacuolation of the cytoplasm of the myelocytes. In black and white these changes are difficult to reproduce. Technic same as in figure 1. Magnification, × 2,000.

pronounced; but, in these cells too, the granules were often clumped together and not sharply differentiated from the cytoplasm. The megakaryocytes appeared intact. The normoblasts varied considerably in size, and some of them were large. The reticular cells were swollen, and many of them contained erythrocytes, normoblasts, degenerated granulocytes and pigment granules.

In the pulp of the spleen there were a few neutrophilic myelocytes and leukocytes the granulation of which showed the same changes as those described in the bone marrow. The pulp was rich in plasma cells and free histiocytes, and there were also a few normoblasts. In the liver the Kupffer cells were much swollen, and many free monocytoid cells were seen in the lumen of the sinusoids. The portal blood vessels contained also single degenerated neutrophilic myelocytes and leukocytes and normoblasts. In the lymph nodes no granulated elements were found. There were much swelling and proliferation of the reticulo-endothelial cells, and the medulla was rich in plasma cells. The necrotic mucosa of the tongue and vagina was not sharply separated from the intact tissue. About the necrosis there were small accumulations of plasma cells, lymphocytes and free histiocytes.

Between these cells a few degenerated neutrophilic leukocytes, fairly well preserved eosinophilic leukocytes and intact mast cells were present.

Case 7.—A white woman, aged 25, deaf, with an illness of eighteen days' duration, entered the hospital in such a serious condition that the history had to be taken from her husband, who reported that she had been well until two weeks before when a severe chill suddenly developed followed by pain in the chest and cough. The sputum was at first mucopurulent and later became blood-tinted. The husband also stated that for the past two years she had been receiving antisyphilitic treatment. The patient's temperature was 104 F. At the inner side of both nostrils there were several red papules, and the right cheek showed a crusted pustule about 1 cm. in diameter. The gums were discolored and covered by a dirty gray, thin membrane. A few lymph nodes could be palpated on both sides of the neck, and about the anus there were many small cauliflower-like masses (condylomata acuminata). The Wassermann reaction of the blood was two plus. The blood cultures proved to be sterile. The blood picture showed: hemoglobin, 75 per cent; erythrocytes, 3,900,000; white cells, 1,900; lymphocytes, 90 per cent; monocytes, 6 per cent, and irritation forms, 4 per cent. The patient died four days after admission.

The pathologic anatomic diagnosis was: gangrenous and ulcerative tonsillitis and pharyngitis; septic tumor of the spleen (weight of the spleen, 650 Gm.); marked cloudy swelling of the liver and the kidneys; ulcerative colitis and typhlitis; pseudomembranous urethritis; hemorrhagic confluent bronchopneumonia in the right upper lobe; cholelithiasis and chronic cholecystitis, and dried necrotic lesions on the right cheek and about the nostrils.

The marrow of the femur was fatty and light yellow. Histologically, there were only a few small islands of cells between the fat cells which amounted to about 1 per cent. These islands consisted of normoblasts (70 per cent), degenerated neutrophilic myelocytes (15 per cent), degenerated oxyphilic myelocytes (3 per cent), lymphocytes (7 per cent), plasma cells (4 per cent) and free histiocytes (1 per cent). The degenerated neutrophilic myelocytes had completely lost their granulation, the cytoplasm was vacuolated, and the nuclei were often broken up into coarse segments. In the oxyphilic granulocytes the granules stained pale red. Many of the plasma cells had pyknotic nuclei. The bone marrow of the ribs was much more cellular than that of the femur, containing 82 per cent myeloid cells, chiefly erythroblasts and normoblasts. The neutrophilic myelocytes appeared better preserved, but only a few of them showed an intact granulation. There were many well preserved young and mature megakaryocytes and megakaryoblasts which formed small groups and were equal in number to the myelocytes.

Outside the bone marrow no granulocytes could be found. The pulp of the spleen contained a few young and mature megakaryocytes and many free histiocytes. The medulla of the lymph nodes was rich in plasma cells. The defense reactions against the ulcerative and necrotic lesions in the pharynx and colon consisted of accumulations of lymphocytes, plasma cells and large, free histiocytes with a vacuolated cytoplasm.

Prolonged Septicemia (Sepsis Lenta) with Agranulocytosis.—Case 8.—A white woman, aged 42, for the past five years had been suffering from frequent attacks of arthritis which, during the last year, became more severe, causing a moderate deformity of the fingers and wrists. Four months before the present illness the patient was in the hospital with a definite attack of cardiac decompensation. Her condition improved, and she went home but returned two months later with

erysipelas of the face. She recovered from the erysipelas, but had several "sinking spells," which she attributed to her heart. Two days before readmission to the hospital she experienced a severe chill followed by many less severe ones. In the last few months she had lost 30 pounds (13.6 Kg.). On admission, the temperature was 105.6 F. The pulse rate was 136, and the respiratory rate 26. The mouth could be opened only with difficulty because of a marked injection of the throat. The tonsils and the posterior wall of the pharynx were covered by a dirty yellow-gray membrane which bled on removal. There was also a marked tenderness and swelling at the right angle of the jaw. The heart was slightly enlarged and a faint systolic blow was heard at the apex. The spleen was distinctly enlarged and the fingers and wrists were much deformed. The blood picture showed: hemoglobin, 35 per cent; erythrocytes, 1,480,000; white blood cells, 600; lymphocytes, 81 per cent; monocytes, 17 per cent; irritation forms, 2 per cent; platelets, 42,000; bleeding time, four and one-half minutes; coagulation time, eighteen minutes. The blood culture showed Streptococcus viridans. (A blood culture taken at home, a month prior to entrance to the hospital, had also shown green streptococci.) The throat culture showed green and hemolytic streptococci. Soon after admission the patient lapsed into coma and died two days later.

The pathologic anatomic diagnosis was: pseudomembranous tonsillitis and pharyngitis; sepsis lenta; acute glomerulonephritis; subicteric discoloration of the skin and sclerae; marked chronic hyperplasia of the spleen (weight of the spleen, 620 Gm.); slight hypertrophy of the heart (weight of the heart, 365 Gm.); cloudy swelling of the liver; severe anemia; deforming arthritis of the finger and wrist joints of both hands; nodose goiter, and a hemorrhagic corpus luteum cyst.

Cultures taken from the spleen yielded green and hemolytic streptococci.

The bone marrow of the femur was soft and dark purple-gray. On microscopic examination the marrow was found much congested, and the reticular cells were markedly swollen and contained many red blood cells. The cell content amounted to 80 per cent. The following cell forms could be distinguished: myeloblasts, 0.2 per cent, and neutrophilic myelocytes, 2 per cent. These cells revealed severe degenerative changes or were completely necrotic. The nucleus was often fairly well preserved (except for the necrotic cells in which no nucleus could be seen). The outlines of the cells were irregular, and the cytoplasm was finely vacuolated, some of the vacuoles staining a light pink. The specific granules were scanty. There were 4 per cent erythrogonia, 20 per cent erythroblasts and 49.5 per cent normoblasts. Among the normoblasts there were single large forms. Examination also disclosed 7 per cent lymphocytes, 3.6 per cent plasma cells, 5.6 per cent monocytoid cells, 2 per cent free histiocytes, 2 per cent megakaryoblasts and 4 per cent megakaryocytes. The megakaryocytes revealed degenerative changes, and some of them were necrotic. In addition to the diffusely scattered lymphocytes, there were many well defined lymph follicles.

In the myocardium typical Aschoff bodies with fibrinoid necrotic center and mononucleated and multinucleated myocytes in fan-shaped arrangement were found. The heart valves were microscopically unchanged. The spleen showed a thickening of the reticulum, much erythrophagocytosis by the reticular cells and many plasma cells and single nucleated red blood cells. In the liver the Kupffer cells were prominent, and the capillaries contained many free histiocytes.

Case 9.—A Negro, aged 52, stated that for the past year he had noted a progressive enlargement and pain, first of his small joints, and then of his large joints. The symptoms gradually spread from the finger joints to the wrist, knee, hip and lumbar joints until practically all the joints were involved. There was a slight remission up to two months before admission to the hospital when the

symptoms became exaggerated, so much so that the patient had to remain in bed and was unable to move. During the last ten months he had lost 45 pounds (20.4 Kg.). He was a heavy drinker, consuming half a pint of whisky a day for two years. On admission his temperature was normal, but during his four weeks' stay in the hospital he had a remittent fever up to 101 F. Examination of the lung and heart gave negative results, and the spleen was not palpable. The essential observations were a marked muscular atrophy with tenderness and limitation of motion. The finger joints were deformed. The Wassermann reaction was negative. The blood picture showed: hemoglobin, 65 per cent; erythrocytes, 3,600,000; white cells, 1,800, and lymphocytes, 82 per cent. The majority of the lymphocytes were larger than the normal small lymphocytes and possessed an ample light blue cytoplasm with scanty azure granules. There were 18 per cent monocytes. While in the hospital the patient had several attacks of sore throat.

The pathologic anatomic diagnosis was: sepsis lenta; moderate generalized anemia; moderate jaundice; deforming arthritis of the fingers, wrists, toes and knees; slight induration of the spleen (weight of the spleen, 150 Gm.); brown atrophy of the heart (weight of the heart, 260 Gm.); fibrous obliteration of the pericardial sac; slight atrophy of the liver; chronic peptic ulcer of the duodenum, and diffuse colloid goiter.

Cultures taken from the heart's blood revealed a pure growth of green streptococci.

The bone marrow of the femur was moderately firm and yellow-gray with purple gray areas. Microscopically, four fifths of it consisted of fat tissue, the rest being formed of myeloid cells. The reticular cells were filled with iron pigment. There were 22 per cent myeloblasts and 22.6 per cent neutrophilic myelocytes. The nuclei of the myelocytes were broken up into coarse chromatin granules. The specific granules were transformed into rose red droplets which seemed to fuse with the pale stained cytoplasm. There were 6.8 per cent neutrophilic granulocytes the granulation of which was indistinct. There were eosinophilic myelocytes (1.4 per cent), eosinophilic leukocytes (0.6 per cent) and basophilic myelocytes (1 per cent). These cells showed a fairly intact granulation. Examination also showed 1.2 per cent erythrogonia, 6.8 per cent erythroblasts, 31.4 per cent normoblasts, 3.6 per cent lymphocytes, 8.8 per cent plasma cells, 12.4 per cent monocytoid cells and 1.2 per cent megakaryocytes.

In the myocardium there were small perivascular accumulations of lymphocytes. The reticular cells of the spleen were filled by erythrocytes and iron pigment, and the cords of the pulp contained many plasma cells and free histiocytes. After a long search, a few neutrophilic leukocytes were found. The liver showed areas of extreme dilatation of the sinusoids in which the Kupffer cells were swollen and proliferated and formed small nests. The periportal tissue was infiltrated by lymphocytes and plasma cells, and there were also a few well preserved oxyphilic leukocytes. The lymph nodes revealed swelling and proliferation of the reticular endothelial cells and much erythrophagocytosis by these cells. In the medulla many plasma cells were present.

COMMENT

In three of the cases of apparently idiopathic agranulocytosis and in one of the cases in which the history suggested relations between the agranulocytosis and antisyphilitic treatment, the bone marrow of the femur was found to be much more cellular than the age of the patients would lead one to expect. In this hyperplasia the granulopoietic tissue

took an active part, and it seems, therefore, that in some instances the agranulocytic catastrophe is preceded by proliferation of the young myelocytes. In the remaining cases the cell content of the bone marrow of the femur was not increased, and the destruction of the granulopoietic tissue did not follow an initial hyperplasia.

In both the hyperplastic and the nonhyperplastic bone marrow the granulopoietic cells revealed severe regressive changes, and it was often only by comparison with the less altered cells that the young myelocytes could be identified as such. Correlating the histologic changes in the different cases, I have obtained the impression that the specific granulation is the first to become affected while the nucleus remains intact for some time and may even divide by mitosis. The specific granules swell, their outlines become indistinct, and small vacuoles often appear around them. The granules later dissolve into these vacuoles, and pale, purple-pink droplets result which fuse together giving a vacuolated appearance to the cells. In the meantime the chromatin of the nuclei has become separated into coarse, sharply defined clumps, and the nucleoli have disappeared. An occasional mitosis may be detected in a cell which has been deprived of its granulation. The mitoses are, however, atypical, with short and clumsy chromosomes, and I think that they do not pass beyond the metaphase. Finally, the nucleus shrinks and disappears, the cytoplasm coagulates and the cell is dead. With the dissolution of the granules into the vacuoles, the oxidase reaction becomes negative. When present, the myeloblasts appear intact, which suggests that therapeutic attempts are not absolutely hopeless even in the acute forms of the disease.

I did not have the opportunity to study the bone marrow in a case of agranulocytosis in which the granulopoietic tissue proved to be intact. The explanations which Reichenbach, Zikowsky and Fitz-Hugh and Krumbhaar offered for these cases sound logical, since it is possible that disturbances in the maturation of the myelocytes or emigration of the mature granulocytes may precede visible changes in the structure of these cells. In this connection, it may be recalled that hyperplasia of the bone marrow has also been found occasionally in cases of aplastic anemia (Gerlach [31] and others). But besides lack of maturation or blockade of the bone marrow, a disproportion between destruction of the mature forms and the supply of new cells has to be taken into consideration. Kracke [32] believes that the bone marrow is affected before the granulocytes disappear from the blood stream. He and Roberts assume with Weiskotten [33] that the normal span of life of a neutrophilic leukocyte is only four days. Whether this holds true for human leuko-

31. Gerlach, W.: München. med. Wchnschr. **79**:1101, 1932.
32. Kracke, R. R.: J. Lab. & Clin. Med. **17**:993, 1932.
33. Weiskotten, H. C.: Am. J. Path. **6**:183, 1930.

cytes remains to be proved. Since the first description of agranulocytosis by Werner Schultz, interest has been focused on the bone marrow, and Naegeli stressed only severe pathologic changes in the nuclei, cytoplasm and granulation of the neutrophilic leukocytes.[33a] I fully agree with Naegeli that the few neutrophilic leukocytes which are occasionally found in the blood films in agranulocythemia are most severely altered. In hemolytic anemia the erythropoietic tissue is most active, and yet the number of the erythrocytes in the peripheral blood is much diminished. Excessive destruction of the erythrocytes can be gaged by the hemosiderosis of the blood-forming organs and by the elimination of the iron and other products of the erythrocyte cleavage. The destruction of the leukocytes does not lead to microscopically visible waste products, but the study of the uric acid metabolism of subjects on a purine-free diet allows certain conclusions as to the extent of leukocytic disintegration (see the interesting studies of Krainick [34] on cases of myelosis). I suggest that such studies be made in cases of agranulocytosis.

The great majority of the cases of agranulocytosis show histologic evidences of a severe injury to the granulopoietic tissue. One may question the significance of the granulolytic processes which I have put in the foreground of my histologic description, and one may consider them as artefacts due to postmortem changes. Undoubtedly a biopsy on bone marrow during life is superior to examination of the bone marrow removed at autopsy (Custer,[35] Dameshek and Ingall and others). The method of biopsy, however, has its limitations. Some investigators will hesitate to perform even a small operation in a case of agranulocytosis, since extensive necrosis of the skin has been observed following the needle wounds made in puncturing the veins of the arms. The small bit of tissue removed from the sternum will hardly allow definite conclusions as to the condition of the bone marrow in general. In case 7, for instance, there was a considerable difference between the bone marrow of the ribs and that of the femur. Furthermore, biopsies necessitate decalcification.

In the majority of the cases on which my studies were based, especially in those in which the pictures were taken, the autopsy was performed within three hours after death. The greatest care was taken in fixing the marrow, and in preparing the sections and the other bone marrow elements, in particular the delicate myeloblasts, hematogonias

33a. In a case of cyclic benign neutropenia, Rutledge and his associates (Bull. Johns Hopkins Hosp. **46**:369 [June] 1930) found a marked decrease in motility of the neutrophilic leukocytes associated with a diminished intake of neutral red just before and during the attack.

34. Krainick, H. G.: Deutsches Arch. f. klin. Med. **172**:70, 1931.

35. Custer, R. P.: Am. J. M. Sc. **185**:617, 1933.

and megakaryoblasts were excellently preserved. When autopsy is performed in cases of septicemia twelve hours or more after death, the granules of the myelocytes often stain poorly or not at all. But there is not the peculiar swelling and dissolution of the granules into vacuoles which I have stressed, and I am therefore inclined to believe that this dissolution is an intravital phenomenon.

In several of my cases the giant cells in the bone marrow were conspicuous. They were increased in number, and many young forms with signs of multiplication were present. Similar observations were made by Koch, Richards, Zikowsky, Hallermann, Petri, Rotter and Uffenorde. It is of particular interest that, besides proliferation, the megakaryocytes often showed evidences of disintegration (fig. 3). Degeneration of the megakaryocytes in cases of agranulocytosis was also described by Rose and Houser, Hartwich, van den Wielen, Zikowsky and others. Hence, in agranulocytosis the alteration is not always restricted to the myelocytes but may involve also the megakaryocytes, which points to transitions to aleukia hemorrhagica (Frank) or thrombopenic granulocytopenia (Kracke).

As far as the erythropoiesis is concerned, a moderate anemia develops usually in cases of more prolonged agranulocytosis (Bock and Wiede [36] and others). According to Brogsitter and von Kress,[37] this anemia does not assume the character of an aplastic anemia. The bone marrow in typical cases of agranulocytosis shows a normal or increased erythropoiesis, and in two of my cases the erythropoiesis went back to the most immature precursors of the red cells, namely, to the erythrogonia. There were, however, some deviations from the normal erythropoiesis. Thus, the normoblasts varied considerably in size, and some of them were large and hyperchromatic. In one case segmentation of the nucleus started before pyknosis was completed, a phenomenon which I have seen in aplastic anemia.

In all the cases which I observed lymphocytes and plasma cells were present in the bone marrow. The percentage of the lymphocytes varied between 0.2 and 27.2, that of the plasma cells between 3.2 and 22.8. In several cases small lymph follicles were found. The reticulohistiocytic elements of the bone marrow were not strikingly affected. In some cases they were slightly hyperplastic with signs of erythrophagocytosis and with iron pigmentation. Free monocytoid and histiocytic cells amounted to from 1 to 12.4 per cent. There was occasionally a net of fibrin between the cells, and in one case the bone marrow contained recent extravasations of blood.

36. Bock, H. E., and Wiede, K.: Folia haemat. **42**:7, 1930.

37. Brogsitter, A. M., and von Kress, H.: Virchows Arch. f. path. Anat. **276**:768, 1930.

Are the changes in the bone marrow in so-called idiopathic or primary agranulocytosis specific? Does the study of the bone marrow support the conception that agranulocytosis is a distinct disease entity which should be separated from the symptomatic forms (W. Schultz, Elkeles,[38] Friedemann,[39] Leon,[40] Licht and Hartmann, Ottenheimer,[41] Stern,[41] Weiss,[41] Piersol and Steinfield,[42] Fitz-Hugh and Comroe, Naegeli, Hueper [43] and others? I think not. Many cases of agranulocytosis have been observed following antisyphilitic treatment (Farley,[44] Hartwich, McCarthy and Wilson,[45] Aubertin and Lévy,[46] Bock and Wiede and others). Two of my cases apparently belong to this group. The bone marrow in these two cases does not differ from the bone marrow in the idiopathic cases, and I can even go a step further and add that there are no differences between the bone marrow in agranulocythemia and that in neutropenic septicemia. Several years ago I expressed the opinion that agranulocytosis is not a disease but a symptom complex [47] (see also Zadek, Dameshek and Ingall, Stocké,[48] Hueber, Rose and Houser, Zikowsky, Hallermann, Reichenbach, Connor, Margolis, Birkeland and Sharp,[49] Barta and Eroes,[50] K. Schultz,[51] Uffenorde and others). This conception is also borne out by the morphology of the bone marrow. The agranulocytosis may be caused by a variety of toxic and infectious agents. In producing the symptom complex, a high virulence of the infecting micro-organisms, a specific affinity of chemical substances for the bone marrow, radiating energy, exhaustion of the bone marrow by continuous overstimulation (sepsis lenta) or a congenital weakness of the leukopoietic tissue may be instrumental. The necrotizing gangrenous lesions of the mucous membranes which follow so quickly the disappearance of the granulocytes from the blood stream render etiologic studies exceedingly difficult. A specific agranulocytic virus has not yet been discovered.

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38. Elkeles: Med. Klin. **20**:1614, 1924.
39. Friedemann, V.: Med. Klin. **19**:1357, 1923.
40. Leon, A.: Deutsches Arch. klin. Med. **143**:118, 1923.
41. Cited by Hartwich.[15]
42. Piersol, G. M., and Steinfield, E.: Arch. Int. Med. **49**:518, 1932.
43. Hueper, W. C.: Arch. Int. Med. **42**:893, 1928.
44. Farley, D. L.: Am. J. M. Sc. **179**:214, 1930.
45. McCarthy, F. P., and Wilson, R.: J. A. M. A. **99**:1557, 1932.
46. Aubertin, C., and Lévy, R.: Ann. de méd. **27**:151, 1930.
47. Jaffé, R. H.: München. med. Wchnschr. **73**:2012, 1926.
48. Stócké, A.: Folia haemat. **40**:40, 1930.
49. Connor, H. M.; Margolis, H. M.; Birkeland, J. W., and Sharp, J. E.: Arch. Int. Med. **49**:123, 1932.
50. Barta, J., and Eroes, G.: Virchows Arch. f. path. Anat. **279**:370, 1930.
51. Schultz, K.: Beitr. z. path. Anat. u. z. allg. Path. **89**:350, 1932.

CONCLUSIONS

The histologic changes of the bone marrow in nine cases of agranulocytosis are described in detail. Five of the cases belong to the group of cases of the so-called idiopathic form of agranulocytosis. Two cases seemed to have developed during antisyphilitic treatment, while the remaining two proved to be cases of prolonged Streptococcus viridans septicemia.

In agranulocytosis the essential pathologic process is a disintegration of the specific granules of the myelocytes which is followed later by pyknosis of the nucleus and death of the cells. Because of the disappearance of the granulation, the myelocytes lose their characteristic appearance. The degeneration of the myelocytes is sometimes preceded by proliferation.

In a considerable number of cases of agranulocytosis the bone marrow giant cells show signs of proliferation and degeneration which suggest relations to the other forms of regressive blood dyscrasia, in particular to aleukia hemorrhagica.

The changes of the bone marrow in agranulocytosis indicate that agranulocytosis is a symptom complex rather than a disease entity.

CEREBRAL ANEURYSMS

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Forbus [1] recently showed that an absence of media is found at the bifurcation of the cerebral and other arteries. In relation to this study, he presented a case in which there were four small aneurysms at the branching of the cerebral vessels. He found no other vascular lesions, and concluded that the aneurysms were congenital. He believed that such miliary or congenital aneurysms developed at the bifurcation of cerebral arteries in a medial defect. Medial defects of the cerebral arteries have been confirmed by Chase [2] and Voncken.[3] The former reported a large aneurysm at the branching of the middle cerebral artery. Since there were no other vascular lesions, he considered the aneurysms congenital and formed in a medial defect. The cerebral aneurysm reported by Voncken was believed by him to be septic but to originate also in a defect of the media. In the present paper are described six cases of aneurysms of the cerebral arteries in relation to the lesions of the vessels of the circle of Willis and their branches.

REPORT OF CASES

CASE 1.—A woman, aged 39, with a history of hypertension of one and a half years' duration, died after gradually increasing weakness. At necropsy multiple hemorrhages throughout the brain and marked atheromatosis of all cerebral vessels were found. A small vessel in aneurysmal dilatation was observed in the meninges of the cerebellum. A similar one in partial rupture extended along the medulla oblongata and the pons. The entire wall of each vessel was composed of hyalin, while the lumen was almost completely occluded from thrombosis. Similar vessels were observed in the hemorrhages of the brain tissue.

CASE 2.—A man, aged 47, died suddenly in the hospital. For three years prior to death he had been under the care of a physician for double vision, pain in the top of the head, ptosis of the right eye and difficulty in walking. On admission to the hospital the knee jerks were absent, and both eyes showed optic atrophy. At necropsy a ruptured, walnut-sized, thrombosed aneurysm was found extending from the site of the branching of the right internal carotid, middle cerebral, posterior communicating and anterior cerebral arteries to a depression 1 cm. in length on the right side of the pons. Marked atheromatous changes

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From the Pathological Laboratory of the Buffalo General Hospital.

1. Forbus, W. D.: Bull. Johns Hopkins Hosp. **47**:239, 1930.
2. Chase, W. H.: J. Path & Bact. **35**:19, 1932.
3. Voncken, J.: Frankfurt. Ztschr. f. Path. **42**:41, 1931.

were observed in the other cerebral arteries. Microscopic examination of the aneurysm showed complete thrombosis and a narrow wall composed entirely of hyaline tissue.

CASE 3.—A man, aged 83, died following gastro-enterostomy for peptic ulcer. At the branching of the anterior communicating and right anterior cerebral arteries was observed a bean-sized, thrombosed aneurysm. Areas of arteriosclerosis were present in the arteries. On microscopic examination, the aneurysm was found to be at the forking of two vessels. The lesions of the intima of these two vessels varied slightly in extent in different sections of the series. In the sections showing the complete formation of the aneurysm were observed split elastic and collagenous fibers in the intima of one vessel. In the intima of the other vessel was a layered formation of split elastic and collagenous fibers with fat cells in the inner part and hyalin with cholesterol in the outer part. At the formation of the aneurysm from the latter artery were found a few collagenous fibers and hyalin in the medial layer. In the intima of the aneurysm were a few split elastic and collagenous fibers which intermingled with the hyalin and collagen of the media to form one layer. The split elastic fibers increased in number, and then became a single strand a short distance to the formation of the aneurysm from the opposite vessel. From this vessel the wall of the aneurysm extended as a short thin layer of hyalin and a few collagenous fibers. At one place in the wall was a pronounced outer thickening of hyalin and fat cells.

CASE 4.—A man, aged 42, was brought to the hospital after a fall in the street. Death occurred in ten days from bronchopneumonia. At necropsy a ruptured, cherry-sized aneurysm was found at the bifurcation of the left middle cerebral artery. Slight atheromatous changes were present in the other cerebral arteries. The relation of the aneurysm to the bifurcating vessels and to the main vessel differed in the various serial sections. Its formation was essentially similar on both sides. Split elastic and collagenous fibers formed the intima at its formation. The elastic fibers then extended for a short distance as a single layer in the outer part of the thin aneurysmal walls. A few muscle fibers, collagenous fibers and hyalin formed the media, which coalesced abruptly with the intima into a single moderately thick layer of collagenous fibers. Transverse sections of the proximate portion of the aneurysm showed in one place a layered formation of split elastic and collagenous fibers underlying collagenous fibers. The remaining portions of the wall were narrow. In one part were fibroblasts and collagenous fibers; in another, hyalin; and in the rest, varying numbers of collagenous fibers with a single strand of elastic tissue. Both sides of the wall were completely disintegrated at the point of rupture. In some of the serial sections, the intima of both bifurcating vessels of the middle cerebral artery showed extensions to the aneurysm. In the intima of one vessel wall were split elastic and collagenous fibers, while in the other was a layered formation of split elastic and collagenous fibers with an inner layer of collagen, fat cells and fibroblasts.

CASE 5.—A man, aged 28, fell and became unconscious while loading milk into a truck. In the hospital bloody spinal fluid was obtained. After four months of rest he began to work lifting cans and fell with a hemiplegia of the right side. At necropsy, a ruptured, thrombosed aneurysm, the size of a walnut, was found at the first branching of the left middle cerebral artery. No pathologic changes were apparent in any other vessel or organ of the body. Microscopic examination of the aneurysm showed at either side of its formation a splitting of the elastic layer, which continued here and there in the aneurysmal wall as a single layer. The media on one side was gradually replaced by hyaline tissue and collagenous fibers. On the other side, the media ceased abruptly in hyaline tissue

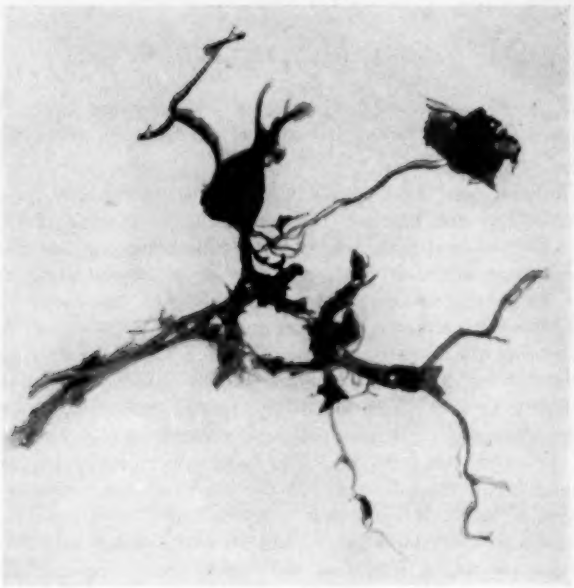

Fig. 1 (case 4).—Ruptured aneurysm in the bifurcation angle of the left middle cerebral artery.

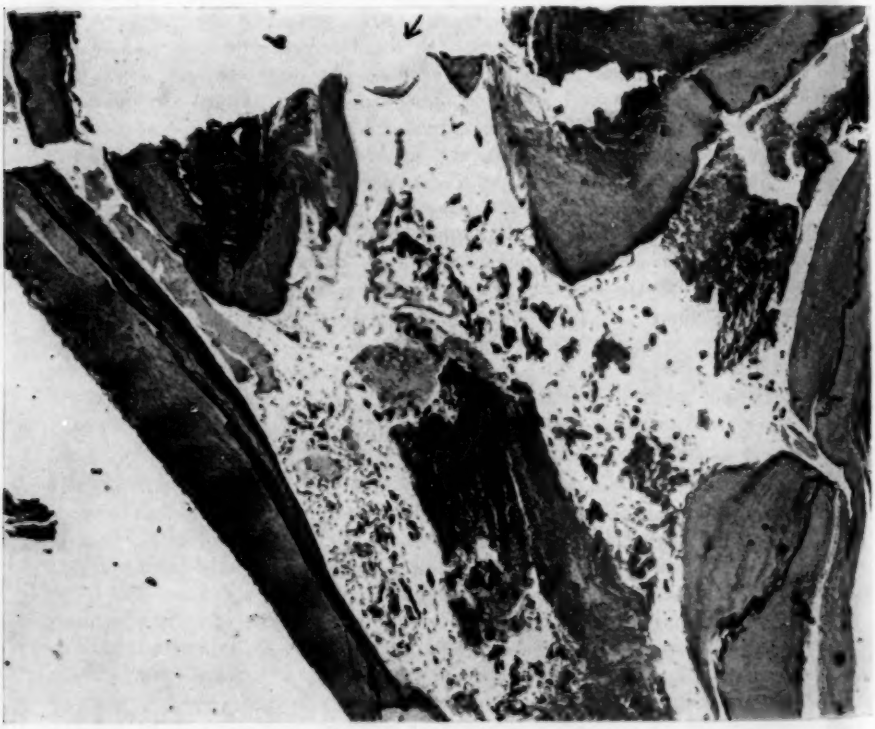

Fig. 2 (case 4).—Formation of an aneurysm in the bifurcation angle. The wall of the aneurysm is partly destroyed.

and then continued as hyalin and collagenous fibers. The intima of the aneurysm was formed of collagen, fat cells, hyalin and cholesterol with granulomatous reaction. The intima and the media gradually formed a single wall of hyaline tissue and collagenous fibers. The adventitia was thickened and showed cellular reaction to previous and present ruptures. The interior of the aneurysm was partially filled with thrombosed blood. The intima of the middle cerebral artery was free from changes except at the formation of the aneurysm, where it became continuous with the inner layer of the aneurysm. The bifurcating artery at the site of the aneurysm showed extensions of collagen and fat cells from the aneurysm. Localized areas of fat absorption were observed at the branching of a small vessel in the basilar artery and at the bifurcation of the right middle cerebral artery. In the other arteries were found an increase in the height and extensions of the areas of split elastic and collagenous fibers at the branchings.

CASE 6.—A man, aged 67, was brought to the hospital in coma. At necropsy a ruptured cherry-sized aneurysm was found at the site of the branching of the left middle cerebral and anterior arteries from the internal carotid artery. The cerebral vessels were thin and smooth except for one small atheromatous area in the basilar artery. Microscopic examination of the aneurysm confirmed its origin in three vessels, which were free from intimal changes except at the formation of the aneurysm. From the intima of one vessel was a short extension of split elastic and collagenous fibers with an inner layer of collagen and fat cells. Both layers terminated in hyaline tissue in which there were no elastic fibers. The media of this vessel ceased abruptly in hyaline tissue which extended for a short distance in the aneurysmal wall. Deeply stained collagenous fibers and fat cells then formed an outer layer to the hyaline tissue of the intima. Extending into the aneurysm from the intima of the other two vessels were collagenous fibers and fat cells which gradually merged into hyaline tissue. The media of these two vessels did not cease abruptly but intermingled with the collagenous fibers. These combined with the intima to form a one-layered growth of hyalin. Split elastic fibers were observed on one side in the outer fat-free collagenous fibers. In the other cerebral vessels not forming the aneurysm was an increase of the split elastic and collagenous fibers in the areas at the branching. The absorption of fat was localized in the macroscopic area at a small branch of the basilar artery.

The cerebral vessels of the six patients with aneurysms and the cerebral vessels of fifty other persons were examined for medial defects. An absence of media was observed at the branching of many small cerebral vessels and at the bifurcation of many large ones. Such absences of media at the bifurcations were observed only once when the muscle fibers in both vessels ran parallel to the elastic layer. They were present when the muscle fibers at the bifurcation were either at right angles or longitudinal to the elastic layer. At all absences of the media the direction of the muscle fibers differed on either side of the omission. Also, the media was never entirely absent. In some serial sections part of the muscle was always present in the defects. An absence of media was frequently observed, not at the branching or bifurcation, but in the wall of a vessel in longitudinal section. At many branches split elastic fibers were seen to spread over and conceal the media. Occasionally split elastic fibers stretched across the media, so that it was loosened from the vessel and gave an appearance of

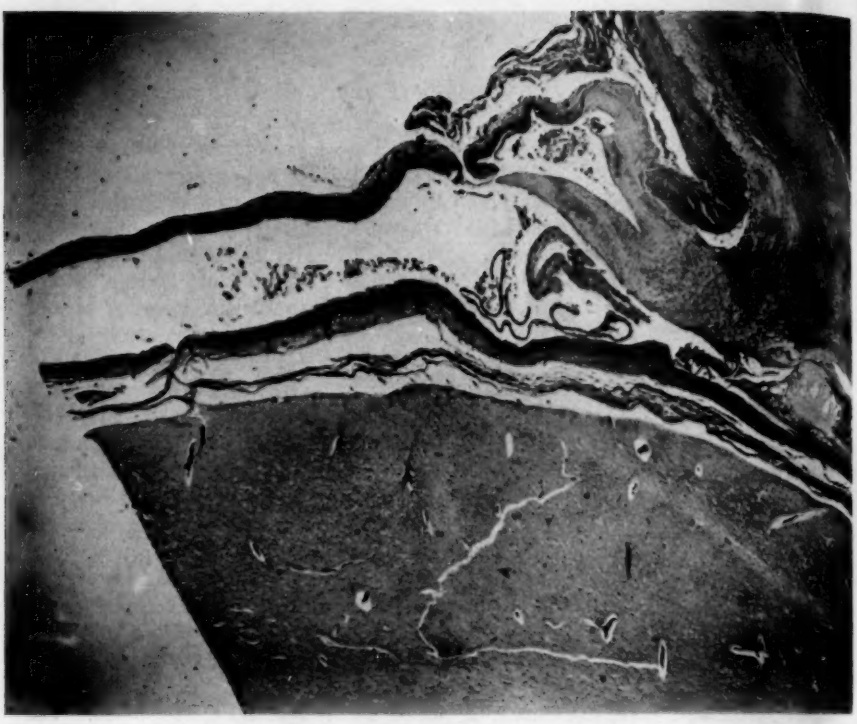

Fig. 3 (case 5).—Absence of arteriosclerosis in the intima of a vessel forming an aneurysm.

Fig. 4 (case 5).—Absorption of fat in an area of split elastic and collagenous fibers at the branching of a cerebral vessel.

being absent. At many branches and bifurcations the media projected at a sharp angle into the lumen, producing bizarre shapes. Split elastic fibers were spread in and around such projections and so cut across them that medial defects were obtained. At many small branches split elastic fibers so covered the media that they appeared to resemble an aneurysm in early formation. The split elastic fibers at some branchings were fragmented and granular, but in further serial sections these fibers became part of the usual area of split elastic and collagenous fibers at the branching.

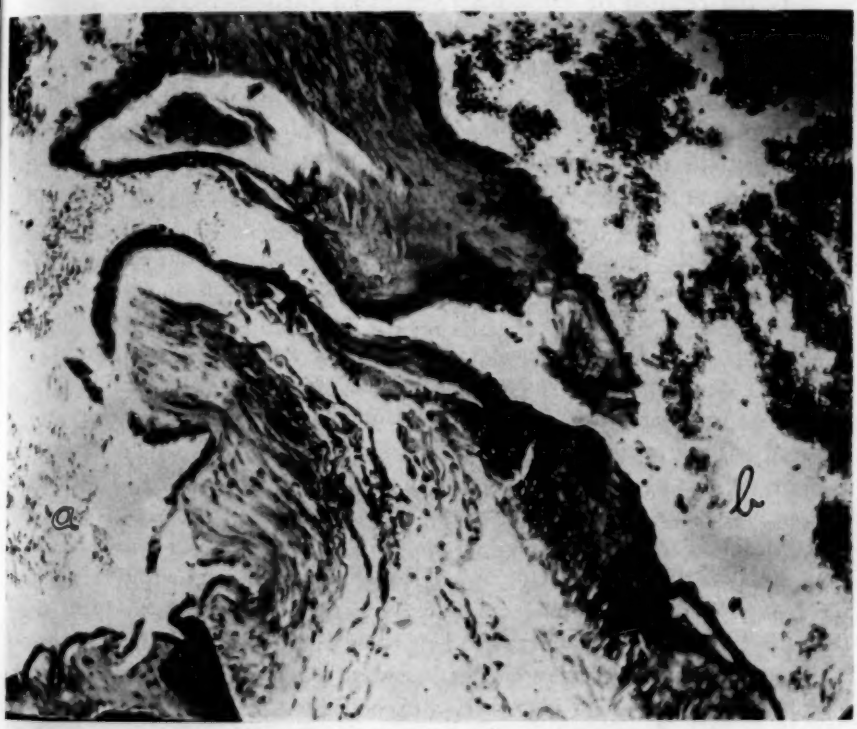

Fig. 5.—Medial defects at the sharp bifurcation of vessels *a* and *b*. There is an apparently artificial loosening of the bifurcation angle as shown by absence of blood cells in intervening space. Nuclei of muscle fibers are seen taking different directions on either side the defect.

COMMENT

Forbus [1] distinguishes a congenital aneurysm from an arteriosclerotic one by the absence of intimal changes in the wall of the vessel from which the aneurysm springs and by the size and location of the aneurysm. Such an aneurysm is small and is situated in the fork of bifurcating vessels. The aneurysm in case 4 in the present series was small and was formed in the center of the bifurcation of the left middle

cerebral artery and would, therefore, appear to be congenital. However, the intima of the bifurcating vessels showed arteriosclerosis, and furthermore these intimal changes were found to unite to the wall of the aneurysm in different sections of the series, suggesting that the aneurysm is not congenital but arteriosclerotic. The aneurysm in case 3 was also similar to a congenital aneurysm, since it was small and was located in the angle of branching vessels. The intima of these two vessels showed old and fresh arteriosclerotic changes which intimate an arteriosclerotic origin of the aneurysm.

If the relation of arteriosclerosis to an aneurysm is established by the change in the intima of the vessels from which the aneurysm arises, in all the presented cases the aneurysms are arteriosclerotic except in cases 5 and 6. In these two cases the vessels forming the aneurysm were free from arteriosclerosis. However, the wall of the aneurysm in the fifth case showed the typical arteriosclerotic growth of collagenous fibers, fat cells, hyalin and cholesterol. The areas of two-layered formation, with hyalin in the outer part and collagen with fat cells in the inner, show that a regressive change from collagen and fat to hyalin takes place as in arteriosclerosis. The wall of the aneurysm in case 6 was similar to that in case 5, except that split elastic fibers were found in the collagenous fibers which were free from fat cells. The walls of these two aneurysms were essentially similar in formation to those in cases 3 and 4. In cases 1 and 2, the aneurysms were composed entirely of hyalin, but hyalin was also present in the other four cases. Forbus [1] believes, however, that the cellular growth in the wall of an aneurysm is not of arteriosclerotic type. He stated that in arteriosclerosis the splitting of the elastic tissue is the final change, whereas in the aneurysm diffuse degeneration and segmentation of the elastic tissue is found underlying intimal thickenings. A study of the elastic tissue in arteriosclerosis shows that the split elastic fibers follow the growth of the collagenous fibers, except when there is a simultaneous growth of fibroblasts, fat cells and collagen. Elastic fibers do not develop in such formations since the absorption of fat tends to destroy collagenous fibers. If fat is absorbed in the split elastic and collagenous fibers, both are destroyed. If split elastic fibers are present in the final arteriosclerotic process, it is because collagenous fibers without fat cells are still present. Their absence in such hyaline tissue or calcium is due either to previous destruction from the absorption of fat or to an inability to develop because the collagenous fibers were quickly destroyed by fat cells. Therefore, the absence or presence of split elastic fibers is determined by the type of arteriosclerotic growth. This appears to be true also of aneurysms, since elastic fibers are absent in hyalin and in collagenous fibers with fat cells but present in fat-free collagenous tissue.

Although Forbus [1] did not describe elastic fibers as occurring in the congenital aneurysms that he observed, one of which had a wall composed entirely of hyalin, the congenital aneurysm recorded by Duguid [4] was formed only of elastic and fibrous tissue. In the congenital aneurysms studied by Chase [2] and Green [5] not only were split elastic fibers present but also fibroblasts, calcium, hyalin and fat as in arteriosclerosis. Schmidt [6] considered eleven of his nineteen aneurysms to be arteriosclerotic, but did not make any distinction in the formation of the walls between an arteriosclerotic aneurysm and those he believed to be congenital. Kerpola [7] divided aneurysms into two classes. In one there is a degeneration of the muscle fibers with a continuous unchanged or split elastic layer. In the other, the media either ceases abruptly at the aneurysm or gradually loses muscle fibers. The intima of the latter group is formed of fibroblastic and split elastic growth which changes into hyalin with a loss of the elastic fibers. He believed that all his cases were arteriosclerotic and suggested that the first change toward the formation of aneurysm is in the media. It is evident that aneurysms are similar in formation, and that they are found in different stages of the same process, which is similar to the intimal growth of arteriosclerosis. The distinction between an arteriosclerotic and a congenital aneurysm cannot, therefore, be made from the formation of the wall.

Although the walls of the aneurysms in cases 5 and 6 were similar to the walls of an arteriosclerotic aneurysm, the absence of arteriosclerosis in the intima of the vessels forming the aneurysm suggests another origin. However, in the cerebral vessel in case 6 was a localized area of fat absorption at the branching of a vessel, while the normally present [8] areas of split elastic and collagenous fibers at the other branches showed a hyperplastic change. Fat was absorbed in several areas at the branching in case 5, while hyperplastic areas were found at the other branches. Since the aneurysms were found at the branching of the vessels, it seems possible that localized absorption of fat occurred in the areas of split elastic and collagenous fibers at these branchings, and that the aneurysms were formed in relation to these arteriosclerotic areas. Schmidt [6] commented on the possibility of a localized arteriosclerosis. Furthermore, the occurrence of arteriosclerotic aneurysms at the branching of the cerebral vessels has been described by Wallesch [9] and others.

4. Duguid, J. B.: J. Path. & Bact. **28**:389, 1925.
5. Green, F. H. K.: Quart. J. Med. **21**:419, 1928.
6. Schmidt, M.: Brain **53**:49, 1931.
7. Kerpola, W.: Arb. a. d. path. Inst. d. Univ. Helsingfors **2**:115, 1919.
8. Tuthill, C. R.: Arch. Neurol. & Psychiat. **26**:268, 1931.
9. Wallesch, E.: Virchows Arch. f. path. Anat. **251**:107, 1924.

A multiplicity of aneurysms also does not distinguish arteriosclerotic from congenital aneurysms, since small multiple arteriosclerotic aneurysms have been reported by McCordock.[10]

Neither the formation of the wall of the aneurysm nor the absence of intimal changes in the vessels forming the aneurysm, nor the size

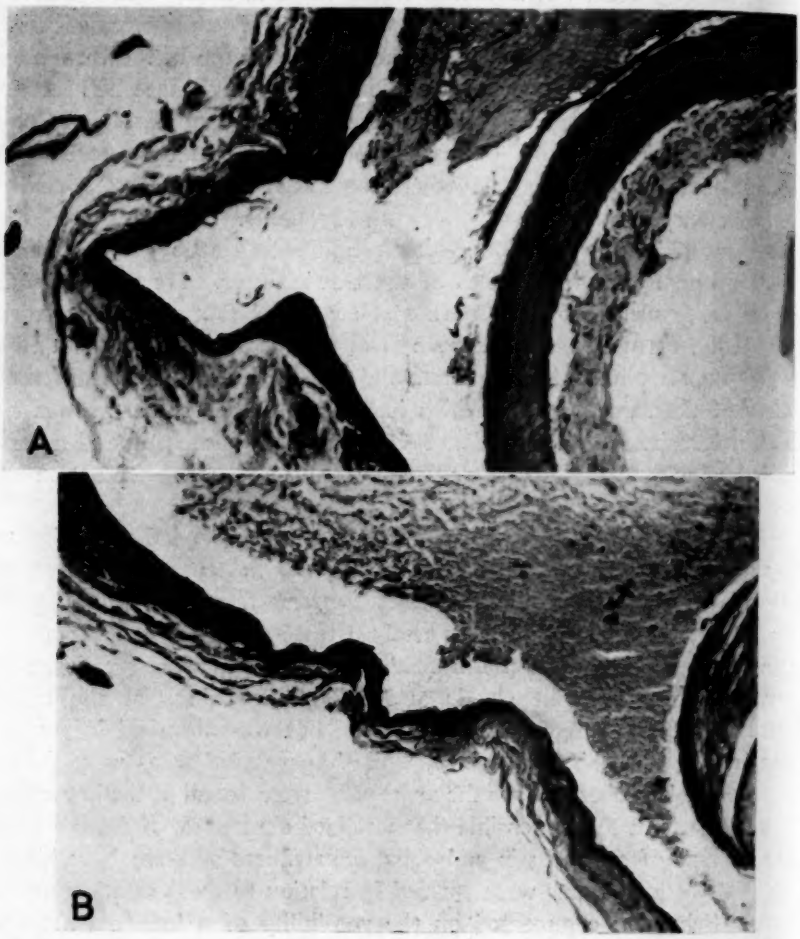

Fig. 6.—*A*, split elastic fibers covering the media at the branching of the vessel; *B*, undercurving of the media and twisting of the vessel before the branching.

and the location of the aneurysm nor the number of aneurysms can serve in determining whether the origin is congenital or arteriosclerotic.

The aneurysms of the small vessels in the first case showed no sacculations as described by Green[11] in small hemorrhages of the brain.

10. McCordock, H. A.: Bull. Buffalo Gen. Hosp. **1**:87, 1923.
11. Green, F. H. K.: J. Path. & Bact. **33**:71, 1930.

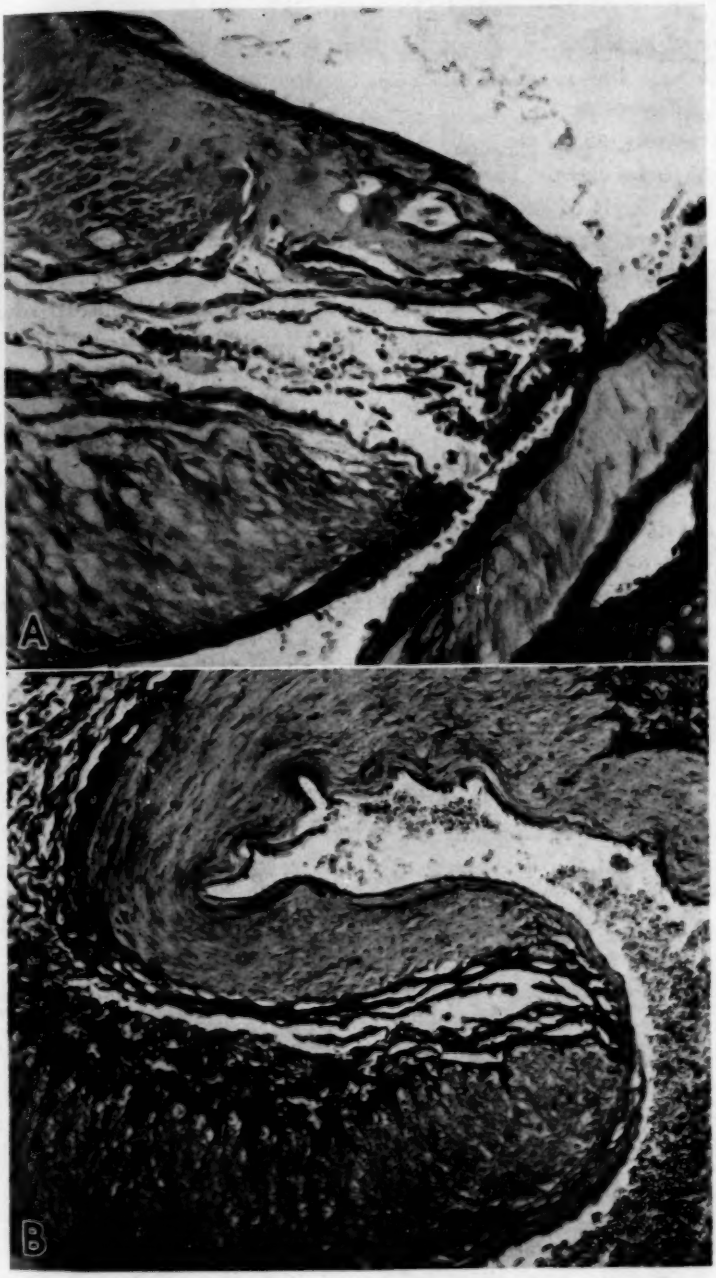

Fig. 7.—*A*, muscle fibers are not running in similar directions on both sides of the defect. There is artificial segmentation of split elastic fibers; a complete area of split elastic fibers at the branching is shown in the succeeding sections. *B*, muscle fibers are shown running in different directions on either side of the defect. The media is rolled under with the elastic fibers bordering the adventitia.

What appeared to be a sacculated aneurysm occurred at the branching of a vessel, but serial sections showed this to be an aneurysmal dilatation of the vessel.

The relation of an aneurysm to so-called medial defects does not appear to be clear. The number of such defects are numerous in the cerebral vessels of each person. If they offer a place of least resistance to blood pressure, it is surprising that aneurysms are not found early in life and in every person. Since cerebral aneurysms are comparatively rare, it is evident that the formation of aneurysms must be due to some primary vascular change rather than to the presence of medial defects only. Furthermore, the existence of a medial defect is difficult to establish. It is apparent that since the cerebral vessels do not run in a plane surface but over an extremely irregular one, they cannot lie in the same plane when embedded, even though injected. A composite picture is therefore necessary in order to see the complete relation of the vessels to each other. The elasticity of the vessels also causes them to twist and to turn in the process of embedding. A proof of such twisting is the rarity of finding the muscle fibers running in the same direction on both sides of a vessel. Such twistings are most pronounced at the bifurcations where the nuclei of the muscles run in a variety of directions. This variation may be considered a normal relation of the muscle fibers, but since it is not regularly found it cannot be due to the growth of the fibers. The absence of similarly directed nuclei on either side of a medial defect also shows that a twisting of the vessels has taken place. It would seem, therefore, that the effect of the twisting and inclination of the vessels at the bifurcations brings the adventitia forward and the media upward, so that only the adventitia and elastic fibers are left at some places in the serial section. This explanation is strengthened by the fact that in the composite picture of the serial sections the media is never wholly absent. If a vessel is twisted throughout its length, the twisting at some point also produces the same medial defect as that at the branching. When the vessels show only slight curving and inclination at the bifurcation, the muscle fibers of the branching vessels tend to run longitudinally with the elastic layer. At such bifurcations are no so-called medial defects unless the angle of branching is too sharp. In such instances projection of the media into the lumen causes the adventitia to be found at some point between the media of the bifurcating vessels, while the elastic layer usually splits over the media. Such sharp angles may also occur at the bifurcation in twisted vessels. At the branching of the vessels, the media may be doubled under so that the adventitia appears in contact with the elastic layer.

Since the medial defects can be considered artefacts, the full explanation of the formation of an aneurysm must be sought elsewhere. The occurrence of light spots in the media underlying fat absorption in the areas at the branching is evidence that the absorption may extend into the media. Since absorption of hyalin succeeds the accumulation of fat, it is suggested that the presence of hyalin in the media at the site of the formation of an aneurysm offers the conclusion that similar changes have preceded the aneurysm. It would appear that absorption

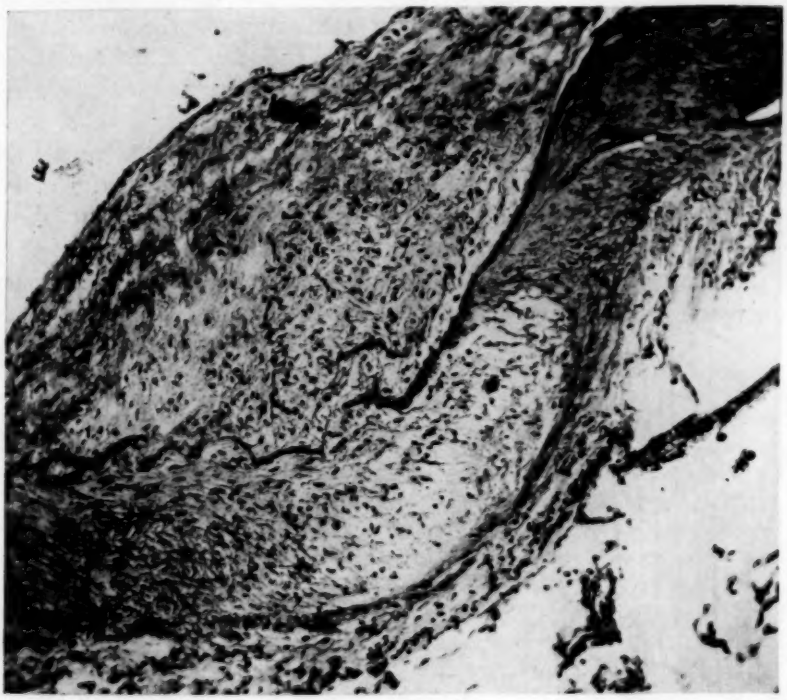

Fig. 8.—Light areas in the media beneath areas of fat absorption in the intima.

of fat in the media causes a weakness of the wall of the vessel which stimulates collagenous growth between the muscle fibers. As the vessel bulges, the intima is extended by a growth of collagenous fibers and possibly split elastic fibers. The absorption of fat leads to the accumulation of hyalin which eventually forms the entire wall.

CONCLUSION

There have been presented five sacculated aneurysms of the large cerebral vessels, varying from the size of a small bean to that of a walnut. Three aneurysms were located at the branching of the vessels;

one in the bifurcation angle of the anterior cerebral and anterior communicating arteries, and one in the angle of the bifurcation of the middle cerebral artery. Various stages of arteriosclerotic changes were observed in the walls of the aneurysms. In two cases there was an absence of arteriosclerotic growth in the intima of the vessels forming the aneurysm. However, these two aneurysms were considered arteriosclerotic because of the hyperplasia of the areas of split elastic and collagenous fibers at the branching of the other cerebral vessels and because of localized absorption of fat in one or more of these areas. In a sixth case were hyaline aneurysmal dilatations of the small arteries of the meninges and of the brain substance with rupture and small hemorrhages. No distinction could be made between arteriosclerotic aneurysms and congenital ones.

The so-called medial defects at the bifurcation of the vessels are explainable as embedding artefacts because of the irregularity of the vascular bed and the twisting of the vessels from elasticity. It is suggested that the absorption of fat in the media underlying the absorption of fat in an area of split elastic and collagenous fibers at the branching of a vessel is the first stage in the formation of an aneurysm.

EXTRAMEDULLARY HEMATOPOIESIS IN A RETROPERITONEAL TUMOR

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Hematopoietic tissue is not uncommonly found apart from the usual sites, in various organs in association with metaplasia of the bone. Extramedullary hematopoiesis, however, has been recorded as a comparatively rare condition and has been the center of considerable discussion for many years. In 1927, Brannan [1] extensively reviewed the literature on this subject, and reported a number of cases occurring in anemic infants. The following case, which recently came under my observation, is of interest in that a large tumor-like mass containing blood-forming elements is a condition infrequently met with in the adult.

REPORT OF CASE

A woman, aged 64, was in good health until one week before admission, at which time cystitis and left-sided pyelonephritis developed. On admission this condition had almost entirely disappeared. On bimanual examination a large globoid tumor mass displacing the rectum could be felt in the left side of the pelvis. A clinical diagnosis of cyst of the broad ligament was made.

At operation a large tumor was found in the hollow of the sacrum, displacing the rectum and sigmoid anteriorly, the bowel lying taut over the anterior surface of the tumor. The tumor occupied the right leaf of the mesosigmoid and was not visible until the peritoneum was incised and about three-fourths inch (2 cm.) of subperitoneal fat was dissected away. By inserting the fingers between the leaves of the mesentery, an encapsulated tumor mass was easily shelled out. Although it was lightly attached to the soft tissues in the hollow of the sacrum just below the promontory, no bony attachments were present. Very little hemorrhage occurred during the operation, the cavity being packed with paraffin gauze, and the abdomen was closed. The patient made an uneventful recovery and was discharged from the hospital two weeks later.

The gross specimen was a roughly globoid mass measuring 11 by 9 by 6.5 cm. and weighing approximately 250 Gm. It was almost entirely enclosed in a thin, glistening capsule which had been somewhat torn on removal. The latter presented a yellowish-gray, translucent appearance with dark brown areas of mottling beneath. A few delicate fibrous tags were adherent to the capsular surface. The tissue was of soft, rubbery consistency and, unlike normal fat, was quite friable and easily fragmented. The cut surface presented a glistening, fatty appearance and was coarsely mottled with irregular chocolate-brown areas suggesting hemorrhage.

From the Department of Pathology, University of Toronto, and the Pathology Laboratories of the Toronto General Hospital.

1. Brannan: Bull. Johns Hopkins Hosp. **41**:104, 1927.

Microscopic sections stained with hematoxylin and eosin and by Giemsa's method revealed a striking picture. In general, all the essential characteristics of bone marrow were present. Evidence of active blood formation, both erythroblastic and leukoblastic, was found in varying degree throughout all the sections examined, the histologic picture being almost indistinguishable from that of normal or somewhat hyperplastic bone marrow. The cellular background was composed of healthy adult fat cells, supported here and there by minute amounts of connective tissue and fairly well supplied by small vascular channels. Scattered throughout the meshwork of fatty tissue were varying numbers of cells, many of which could be definitely recognized as immature forms of both the red and the white series. Sections stained by Giemsa's method showed easily recognizable myelocytes of all

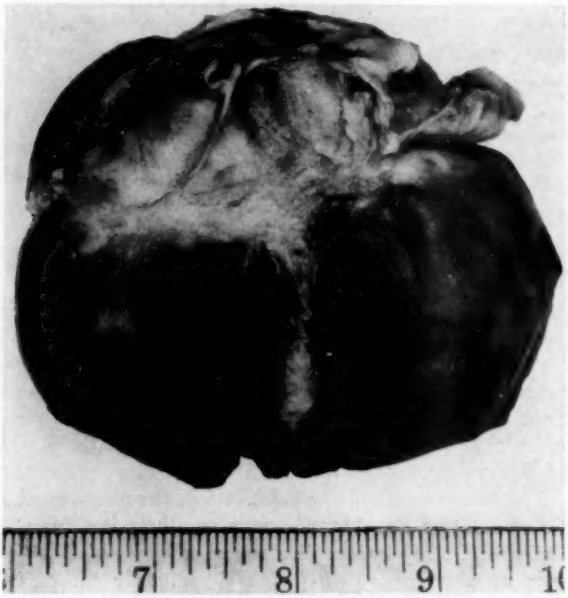

Fig. 1.—Gross specimen of retroperitoneal tumor.

three varieties. Eosinophilic myelocytes, the granules of which stood out with great clearness, formed a striking part of the microscopic picture. Sections stained by the oxydase method showed that many of the cells contained indole-blue granules (positive). Of the erythroblastic series, frequent normoblasts in varying stages of development were present throughout the sections. A few of these cells were found to be undergoing mitotic division. Numbers of quite large and very immature cells with rounded nuclei and varying amounts of basophilic nongranular cytoplasm were seen. The degree of differentiation of these forms made histologic identification impossible.

In the more cellular areas, which corresponded in appearance to active bone marrow, numbers of large, multinucleated forms interpreted as megakaryocytes were found. In some localities these were very numerous, as many as eight occurring in a single low power field. However, in many of the sections in which

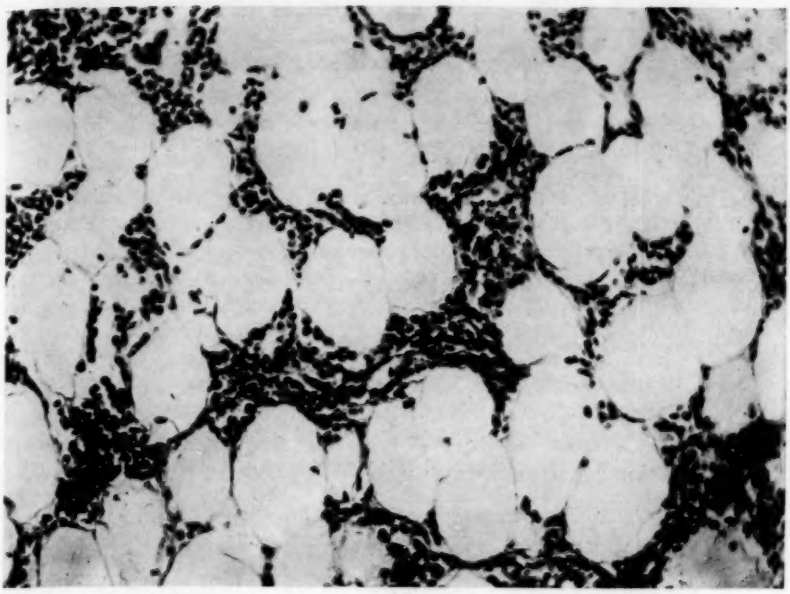

Fig. 2.—The general structure of the tumor, showing its similarity to bone marrow. Groups of blood-forming cells are lying within adipose tissue; × 160.

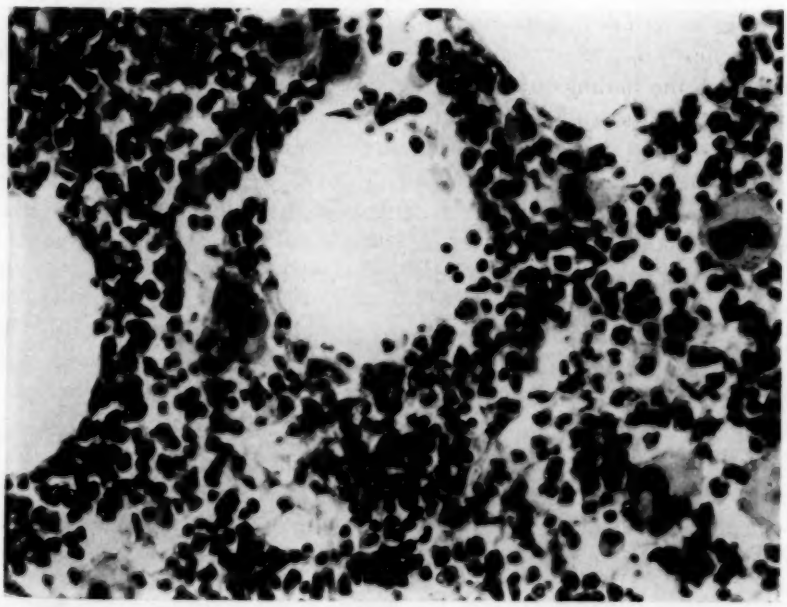

Fig. 3.—A higher magnification, to show more clearly the character of the cells infiltrating the fatty tissue meshwork. The megakaryocytes are quite numerous and prominent in this special region.

hematopoiesis was less active, these cells were met with much less frequently and were often entirely absent.

Varying numbers of red blood cells were found lying between the fat cells, either in association with or entirely apart from areas of blood formation. Throughout the sections considerable activity on the part of the capillary endothelium was observed, with the formation and opening up of many new vascular channels. Small amounts of brownish pigment material which with Perl's stain was found to be iron-containing pointed also to blood destruction taking place to some degree in the tissues. These deposits of hemosiderin were, however, small and scattered, practically all the iron-containing pigment having been phagocytosed by large endothelial cells. Fairly numerous lymphocytes and a few plasma cells were to be seen. In some regions the former were aggregated in small clusters, which did not, however, have the appearance of lymph follicles and did not present germinal centers.

Although the degree of hematopoietic activity varied considerably in different areas, this process was quite apparent in all parts of the tumor examined.

The occurrence of extramedullary blood formation is to be regarded as a purely compensatory mechanism in many cases in which, as the result of destruction, dysfunction or excessive requirements, the bone marrow is unable to meet the demands imposed on it. This is not uncommonly seen where extensive replacement of the marrow by tumor has occurred; Askanazy [2] has described myeloid changes in the liver and the spleen in such conditions. Similar hematopoietic activity in these and other organs has been noted by several observers in various infectious diseases as well as in pernicious anemia, lead poisoning, chronic nephritis and hemochromatosis. In view of the unusual site in the case just reviewed, the findings of Petri [3] are of especial significance. In a series of forty adults, suffering chiefly from acute infections, the majority presented small patches of hematopoietic tissue in the retroperitoneal fat.

Brannan [1] and others have shown that in some of the severe anemias of infants, particularly in the type described by von Jaksch and Luzet, collections of hematopoietic tissue at the renal hili are almost a constant finding, and are also occasionally observed in the liver, spleen, lymph nodes, lungs and dura.

In all the aforementioned cases the formation of blood may be regarded as a compensatory phenomenon. Sometimes, however, it seems that extramedullary blood formation may occur independently of either pathologic conditions of the bone marrow or excessive demands. Saleeby [4] reported a case in which two small masses of hematopoietic tissue were present in the pleura on either side of the chest of a patient presenting no evidence of anemia. Brannan [1] also found small foci of blood formation in the breasts and in the broad ligaments of infants not suffering from anemia.

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2. Askanazy: Verhandl. d. deutsch. path. Gesellsch. **7**:58, 1904.
3. Petri: Virchows Arch. f. path. Anat. **258**:37, 1925.
4. Saleeby: Am. J. Path. **1**:69, 1925.

A review of the literature discloses only three cases similar to that under discusssion. Brannan quoted Rich as having found a kidney-sized mass of bone marrow tissue in the thorax of a patient dying of hemolytic jaundice, and Saleeby mentioned a somewhat similar mass occurring in the pleura in a case of osteitis fibrosa cystica. Hofstätter and Schnitzler [5] discovered a large retroperitoneal tumor in a woman suffering from anemia. This tissue, which showed evidence of blood-forming activity, was attached to, and possibly arose from, the pelvis of the kidney.

The case under discussion offers two important questions for consideration: (1) What is the mode of origin of hematopoietic tissue in this unusual location? and (2) May such a condition be regarded as a compensatory phenomenon? Ziegler, Ribbert and others believed that embolic masses of cells may occasionally be carried by the blood stream from the bone marrow to various parts of the body and set up "metastatic" foci of blood-forming tissue. It has been felt by most observers, however, that these masses arise from remnants of cells and probably represent the sites of embryonic blood formation.

The latter is probably to be looked on as a fairly widespread process, and the possibility of the retroperitoneal fatty tissue being one of the sites in which this occurs must be considered. The observation of Petri [3] that blood formation in this locality is a common finding in acute infections lends support to this view. Warren [6] reported a highly malignant tumor growth having the appearance of bone marrow which he believed originated in the retroperitoneal fatty tissues.

The majority of the cases mentioned in the literature have been associated with anemia of varying degree. The anemia may be regarded as the response to a deficiency on the part of the blood-forming tissues, although isolated instances have been observed in which such a condition did not exist. In the case under discussion the patient suffered from mild secondary anemia. Hematologic examination a few days following operation showed: hemoglobin, 70 per cent; red blood cells, 3,700,000, and white blood cells, 4,300. No apparent cause for the anemia was found. The blood smears showed a normal differential count, with little evidence of variation in the size or the shape of the red cells, a few of which presented slight polychromatophilia. Evidence of active regeneration, however, was found in an increased proportion of reticulocytes, constituting about 7 per cent of the red cells. Although a hematologic investigation was not carried out prior to operation, the amount of blood lost during the procedure could hardly account for the anemia.

5. Hofstätter and Schnitzler: Arch. f. klin. Chir. **140**:567, 1926.
6. Warren: Am. J. Path. **4**:51, 1928.

In this case it is probable that extramedullary hematopoiesis is not to be regarded as a strictly compensatory mechanism in the sense that the bone marrow was inadequate in the demands for increased production of blood. It seems more likely that, in the presence of slight anemia, tissues still retaining the embryologic potentialities of hematopoiesis responded to the same stimulus which called forth a hyperplasia in the bone marrow.

CONCLUSIONS

A large lipomatous tumor of the retroperitoneal tissues containing all the blood-forming elements of the bone marrow has been described.

As the retroperitoneal fatty tissues probably represent one of the sites of blood formation in the embryo, it is probable that the tumor arose from embryologic cell rests or from tissues still having the potentiality of blood formation.

Under increased functional demands, such tissues will respond to the same stimulus as normal bone marrow and will assume the function of production of blood.

A MALIGNANT NEURINOMA (SCHWANNOMA) WITH EPITHELIAL ELEMENTS

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Tumors arising from peripheral nerves in which epithelial elements were present have been reported by Cohn,[1] Stewart and Copeland [2] and Masson.[3] The presence of such elements is in favor of the point of view that these tumors arise from the sheath of Schwann, which is of ectodermal origin, rather than from the endoneurium or the perineurium, which are mesodermal structures. Nageotte [4] and Masson [3] pointed out the similarities between spontaneously occurring tumors of nerves, experimentally produced schwannomas and regenerating nerves. Verocay [5] described circumscribed proliferations of Schwann's cells which he believed were the forerunners of these tumors. He stressed the variations in the staining of the fibrils with van Gieson's stain; and Masson also demonstrated that many of them stain differently than true collagenous fibers with trichrome stains. There is considerable evidence which suggests that many of these tumors arise from the neurilemma and that the collagenous-like fibers in these tumors and the endoneurium in normal nerves in part may be formed by the Schwann cells. One can explain the presence of epithelium-like structures in some of these tumors much more readily on the supposition that they arise from the neurilemma rather than from the mesodermal elements.

It is generally agreed that the neurilemma is of neuro-ectodermal origin, as demonstrated by Harrison.[6] The earlier stages of development of these tumors offer better opportunities for study as to their origin than do later stages, in which, as has been suggested, there may have been a secondary proliferation of connective tissue replacing the neoplastic Schwann cells similar to the replacement of epithelial cells in a scirrhous carcinoma of the stomach.

The case that I shall report is of interest from several angles. Clinically the tumor was of rapid growth, and pain, the chief symptom, was

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From the Department of Pathology of Baylor University College of Medicine.

1. Cohn, I.: Arch. Surg. **17**:117, 1928.
2. Stewart, F. W., and Copeland, M. M.: Am. J. Cancer **15**:1325, 1931.
3. Masson, P.: Am. J. Path. **8**:367, 1932.
4. Nageotte, J., in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, p. 191.
5. Verocay, J.: Beitr. z. path. Anat. u. z. allg. Path. **48**:1, 1910.
6. Harrison, R. G.: Am. J. Anat. **5**:121, 1905.

present for five months. Histologically the tumor presented features of a neurogenic sarcoma throughout which there were scattered small masses of epithelial-like cells. Metastases involved the regional lymph nodes and the lungs particularly and were composed of cells like those in the epithelial masses in the primary tumor. Myxomatous degeneration was a marked feature, especially in the central portion of the primary tumor and less so in the metastases.

REPORT OF A CASE

A white man, aged 73, complained of pain in the left thigh and hip of five months' duration. The pain had been more or less continuous and was described as throbbing, occasionally radiating to the leg and ankle. It became increasingly severe. A tumor was not noticed by the patient until several months after the onset of pain, but by the time of admission to the hospital a large mass was palpable in the left thigh. Urinary obstruction developed two weeks before admission, which was relieved by catheterization but recurred four days previous to admission. There was considerable loss of weight during the five months, owing in part to the extreme pain.

Examination showed a man about 75 years of age who was moderately emaciated. The blood pressure was 132 systolic and 84 diastolic, and the heart and lungs were essentially normal. The left thigh was about 4 cm. greater in diameter than the right. In the medial aspect of the proximal half of the left thigh, was a large, movable mass which extended to a point about 17 cm. below the left groin. A soft, semifluctuant area in the central portion of the mass was aspirated, and a gelatinous, slightly blood-tinged material was obtained. This material contained 3.3 per cent albumin, an occasional polymorphonuclear cell and rarer large, irregular cells with deeply stained nuclei and nucleoli. Pressure over the sciatic nerve elicited some pain, but pressure over the tumor was more painful. The prostate gland was slightly large, firm and moderately tender. Roentgenograms revealed slight mottling and increased density in the region of the left hip. Motion of the leg was not limited.

The man continued to lose weight. The tumor increased considerably in size while the patient was in the hospital, and death occurred on the forty-seventh day. A carcinoma of the prostate was suspected clinically.

Necropsy revealed marked emaciation, moderate anemia and slight edema of the subcutaneous tissues of the feet and ankles. The muscles of the lower extremities were equally atrophic. Both testicles were in the scrotum, of equal size, freely movable and free from gross changes on section. Innumerable firm, grayish nodules, from 1 to 15 mm. in diameter, were present in the peripheral portions in all lobes of both lungs; they were most numerous in the lower lobes. Some of the larger nodules were umbilicated. The mucosal lining of the bronchi and larger branches was free from gross change other than a slight hyperemia. The mediastinal lymph nodes revealed only moderate anthracosis. The rectum was displaced toward the right by a tumor protruding into the pelvis on the left side. The rectal mucosa was intact and free from noticeable changes. The prostate was moderately enlarged, uniformly nodular, firm and grayish pink. The left seminal vesicle was surrounded by an increased amount of fibrous tissue. The left iliac lymph glands were enlarged, some being as large as 2 by 3 by 3.5 cm. All except those showing large, yellowish areas of necrosis were firm. In the smaller glands, small grayish areas could be seen in the peripheral portions. The

lower aortic glands were slightly enlarged. The right inguinal and iliac glands were not enlarged.

The tumor in the left thigh measured 10 by 12 by 20 cm.; it was roughly ovoid and slightly lobulated. The proximal third was smaller in diameter and continuous with the mass in the pelvis. The mass was encapsulated and surrounded by stretched adductor muscles that were easily separated from it. The upper portion was fixed by the pelvis, but the lower portion could be moved with the muscles. The pelvic portion was covered by smooth peritoneum. The consistency varied considerably. On section, the softer areas were composed of a structureless, grayish, gelatinoid substance. The firmer areas appeared to consist of intertwining bands of lighter gray with a tendency to whorl formation. Small reddish-brown areas were present in the soft portions. Several small cystlike areas were also present in the more central portions. The pelvic nerves were

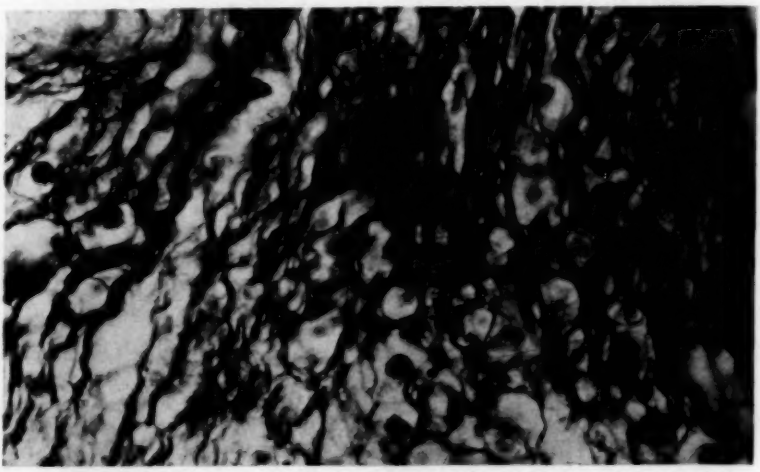

Fig. 1.—Section from an area rich in parallel strands of fibrils of varying caliber. Large cells can be seen between the parallel fibrils which have undergone marked degenerative changes. Laidlaw's silver stain; reduced from a magnification of × 2,400.

not involved except that they were pushed aside by the tumor. The urinary bladder was not involved except for diffuse cystitis. The pelvic bones and the femur were free from gross changes.

Histologic examination of the tumor in the thigh gave rather confusing results, but definitely ruled out certain possibilities. The greater portion was composed of a sarcomatous-appearing stroma presenting features seen in neurogenic sarcomas. Intertwining bundles of elongated fibrils with varying numbers of nuclei, some of which were very much elongated, were seen in the compact areas. Some of these bundles of fibers were much swollen and had compressed the surrounding tissue slightly. This swelling seems to have been due to myxomatous degeneration, which was marked, especially in the more central portions of the

tumor. The length and the thickness of the fibrils varied markedly. Many small fine fibrils could be seen between parallel coarse fibrils (fig. 1). With van Gieson's stain there was considerable variation in the tinctorial reaction, which ranged from yellow to orange to deep red. In the photomicrograph, cells in varying stages of degeneration can be seen between parallel fibers. The fibers were applied to the surface of the cell so that it appeared as though they were laid down along the surface of the cell columns in an arrangement similar to that described by Masson for experimental schwannomas. In some regions a suggestion of a palisade arrangement of nuclei can be seen.

Some long fibrils were not directly associated with nuclei, whereas others had several associated with them in linear fashion. Many of the nuclei were elongated, at times bent on themselves and frequently

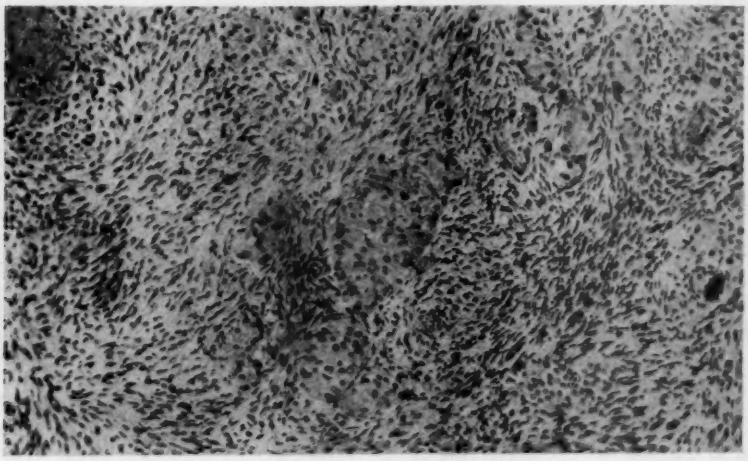

Fig. 2.—Low power magnification of a section which shows the epithelial masses, some of which are considerably elongated. The peripheral nuclei are seen to be perpendicularly arranged. The stroma is composed of cells with elongated nuclei showing a slight tendency toward palisade arrangement. Hematoxylin and eosin.

fissured and irregular in contour. Nucleoli were prominent in a large number of these cells. The number of nuclei varied considerably in different regions. In more cellular areas many nuclei were hyperchromatic, and mitotic figures were present in moderate numbers. The cells varied much in size and shape. Not infrequently nucleated cytoplasmic masses were connected by cytoplasmic processes, which suggested a syncytial character of some portions of the tumor. With such a structure it is possible that many of the rather broad and also of the fine fibrils were derived from these cytoplasmic masses. About some of the blood vessels the arrangement of the fibrils was similar to that in reticulated areas in other tumors of peripheral nerves.

A most interesting histologic feature of the tumor was the presence of fairly uniformly distributed round, oval and elongated epithelial-like masses (fig. 2). Some of these were solid masses composed of cells that simulated pavement cells; others had cuboidal and flattened cells arranged about a lumen. In some instances long, narrow, solid cords of epithelial cells were seen which must have been longitudinal segments of the tubular structures. The nuclei in some of these solid masses were perpendicularly arranged (fig. 2) and were interesting in comparison with a similar feature in the embryonic Schwann membrane (Nageotte [4]). The tubular arrangement may be similar to the behavior of the Schwann cells in developing and regenerating nerves, as pointed out by Masson. The histologic appearance of many of these cells was similar to that of some scattered through the stroma. This applies in particular to the nuclei. Degenerative changes were marked in many. There appeared to be a transition of some of these epithelial masses into the surrounding stroma, strongly suggesting that the epithelial-like cells, in part at least, made up the stroma. In such areas there was an increase in cellularity, in hyperchromatism and in mitoses. The nuclei of many of the cells in such areas were very irregular, frequently being lobulated as though they were undergoing amitotic division. Giant cells were seen in these areas. Keratinization could not be demonstrated in any of the epithelial-like masses.

Blood vessels were moderately numerous. Their walls varied in thickness from those apparently consisting of only an endothelial layer to others that were rather thick and hyalinized. A few vessels were partially or completely occluded by thrombi composed mainly of fibrin and red cells, but in several regions a moderate number of polymorphonuclear cells were seen in the thrombus and the surrounding area. Small hemorrhages were found scattered throughout the tumor. Changes in the vessels similar to these are seen in some of the central gliomas.

The metastases in the lymph glands (fig. 3) were composed entirely of cells similar to the epithelial-like cells in the tumor in the thigh. The cells were large; their borders were frequently indistinct, and in many of them the cytoplasm was vacuolated. The nuclei were large, irregular and frequently lobulated or fissured, with prominent nucleoli. Small areas with a myxomatous appearance similar to the stroma of the main tumor were seen in several of the nodules in the lung, demonstrating that the epithelial-like metastases had undergone changes similar to those in the primary tumor. The metastases in the lungs also contained only the epithelial-like cells. Extensive central necrosis had occurred in the largest nodes.

The prostate was carefully examined but revealed no evidence of malignant change in the epithelium. In adenomatous areas many of the acini were considerably dilated and contained corpora amylacea. In

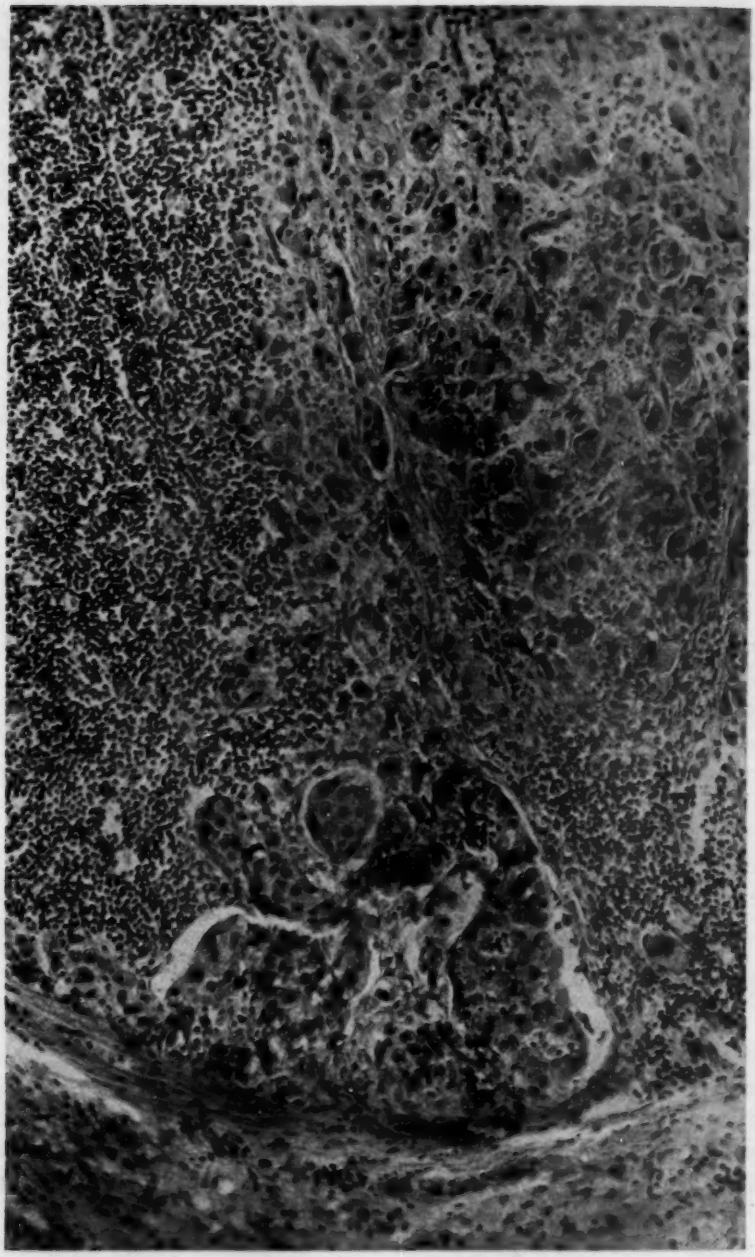

Fig. 3.—Metastatic nodules in a regional lymph node are composed of cells similar to those in the epithelial masses in the primary tumor. Hematoxylin and eosin.

several blood vessels small masses of tumor cells similar to those in the tumor of the thigh were seen. These cells were, however, entirely within the blood vessels. The examination of the prostate definitely ruled out this organ as the seat of a primary malignant growth. The epithelium was regular in its relationship to the stroma, and the cells were uniform. The tumor in the thigh was not one of a type that could be secondary to a primary carcinoma of the prostate. The epithelium, and particularly the stroma, were very different from those of prostatic carcinoma. The unilateral involvement of the pelvic lymph nodes is more in favor of a primary tumor in the thigh.

A primary carcinoma of the lung could produce metastases in a neurogenic sarcoma of the thigh. The bilateral peripheral involvement of the lungs by innumerable small nodules in the peripheral portion of all lobes is against such an interpretation. The bronchi were free from involvement, as were also the mediastinal lymph nodes. The metastatic involvement of the left iliac lymph nodes was of longer duration than that in the lungs because of the greater amount of necrosis, and also the greater proliferation of connective tissue about some of the nodules. It would be unusual for a primary tumor of the lung to select a neurogenic sarcoma in the thigh as a favorite and almost the only site of metastasis.

A teratoma in the thigh might possibly give rise to the lesions found in this case. In such a tumor, however, the small, scattered epithelial masses that were seen throughout the mass would be unusual. If the primary growth were a teratoma one would be forced to admit that both the epithelium and the stroma were malignant, the latter most highly so, but that only the epithelial element had metastasized, which would be unlikely. Other types of tissue are commonly found in teratomas but were absent in this tumor.

Tumors arising from synovial membranes may contain epithelial-like areas. Such tumors have been reported by Smith.[7] The structural arrangement and the appearance of the cells and of the fibrils differ from those of the tumor reported here. There was no connection with a synovial membrane of either the knee or the hip in this case. The changes in the vessels and the presence of numerous vascular spaces might suggest an endothelial origin. These changes were not as marked, however, as in other tumors not of endothelial origin, and the cells did not simulate those seen in endothelial tumors. In a sarcoma arising from muscles, fascia or osseous epithelial elements like those present in this tumor are not found.

The general features of the tumor strongly suggest a neurogenic origin. It was encapsulated and irregularly lobular and ovoid and had

7. Smith, L. W.: Am. J. Path. **3**:355, 1927.

undergone myxomatous degeneration to a marked degree. The arrangement in bundles of fibrils and nuclei, with some tendency toward a palisade arrangement of nuclei, and the reticulated areas are seen in neurogenic tumors. These features are naturally not as evident in a neurogenic sarcoma. The presence of the epithelial-like elements can be explained as masses of Schwann's cells which may assume epithelial-like characteristics because the sheath of Schwann is derived from the embryonic ectoderm. Epithelial elements have been found in nerves and in tumors derived from nerves by others, and have been explained on that basis. Many histologic features in this case fit in with descriptions of experimental schwannomas given by Masson and Nageotte. Tumors of this type strongly suggest that they are derived from the sheath of Schwann and that this sheath can give rise to collagenous-like fibers. In interstitial hypertrophic neuritis of Dejerine and Sotta there is a progressive increase in interstitial tissue which some authors consider as due to a proliferation of the Schwann cells.[8] The neurogenic sarcomas as a rule do not metastasize to the lymph nodes, and metastases occur late, but in a tumor in which along with rapid growth there is marked degeneration, cells may be liberated into the blood and the lymph spaces more readily. Cells with long processes could not be so readily freed from their locations.

CONCLUSIONS

A solitary tumor occurring in the thigh with many features similar to schwannomas described by other authors is reported.

The clinical features of note were severe pain in the thigh of five months' duration and the rapid increase in size of the tumor.

Histologic study indicated that the epithelial-like structures were the most important elements of the tumor and that they, in part at least, if not entirely, gave rise to the stroma.

The rapid growth and the associated degeneration were probably important in the production of metastases.

It was considered worth while to report this case because the growth represents an early stage of development of this type of tumor.

8. Wolf, A.; Rubinowitz, A. H., and Burchell, S. C.: Bull. Neurol. Inst. New York **2**:373, 1932.

COMPENSATORY HYPERTROPHY OF THE THYROID GLAND IN GUINEA-PIGS

EFFECT OF POTASSIUM IODIDE AND OF ANTERIOR LOBE PITUITARY EXTRACT

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In the present investigations I have carried out two series of experiments. In the first the experiments of Loeb, who had shown that the feeding of potassium iodide in small doses to guinea-pigs on the average increased compensatory hypertrophy of the thyroid gland, were repeated. It was desired particularly to determine whether if after the administration of such doses compensatory hypertrophy occurred it was accompanied by an increased number of mitoses, a question which previous investigations had not decided. In the second series the effect of anterior lobe pituitary on compensatory hypertrophy of the thyroid gland in guinea-pigs was studied. In particular was it wished to determine whether the original size of the gland was more readily reestablished following the administration of anterior lobe pituitary. In order to effect compensatory hypertrophy of the thyroid gland, one whole lobe and two thirds or three fourths of the remaining lobe were extirpated.

EFFECT OF POTASSIUM IODIDE

In several series of investigations Loeb [1] and later Gray,[2] in this laboratory, showed that the feeding of potassium iodide to guinea-pigs in which a great part (from one and two-thirds to one and four-fifths lobes) of the thyroid gland has been extirpated does not prevent or even diminish the resultant hypertrophy of the gland, but that on the contrary the occurrence of hypertrophy is more frequent and thus the average degree of hypertrophy is greater than in animals which have not received potassium iodide. Doses varying between 0.1 and 0.01 Gm., especially the daily administration of 0.05 or 0.01 Gm., were effective. However, certain variable factors enter into this type of experiments; thus a loss in weight during the period following the operation was found to be unfavorable for the production of marked hypertrophy.

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1. Loeb, Leo: J. M. Research **40**:199, 1919; **41**:481, 1920; Am. J. Path. **2**:19, 1926; **5**:71 and 79, 1929.

2. Gray, S. H.: J. M. Research **5**:415, 1929.

In the present investigations these experiments were continued and extended; in particular it was desired to determine whether smaller doses of potassium iodide also had an effect on compensatory hypertrophy. Furthermore, it was desired to determine whether if after the administration of such doses compensatory hypertrophy occurred it was accompanied by an increased number of mitoses.

Two series of guinea-pigs were given, for ten and twenty days, respectively, daily oral doses of 0.1, 0.005 and 0.002 Gm. of potassium iodide in the form of pills. The feeding was begun one day after one and two-thirds lobes of the thyroid gland had been extirpated, and the animals were killed one day after the last dose had been given, the remnants of the gland being removed at that time and then sectioned serially. Mitoses were counted in four pieces of the gland in each animal in the control series as well as in each of the animals to which potassium iodide had been administered. As a rule, the mitoses were counted in five sections in each piece. This was sufficient to give an approximate estimate of the number present.

Series A.—Twenty doses of potassium iodide were administered during a period of twenty days following partial thyroidectomy.

Group 1 (Controls).—The greater part of the thyroid gland was extirpated, but the animals did not receive potassium iodide.

Eight guinea-pigs, weighing from 170 to 205 Gm., with an average weight of 190.6 Gm., were used. Seven animals gained on the average 16.1 per cent, while one lost 15 per cent, of the original weight. The average number of mitoses in the remaining parts of the glands was 240.

The average degree of hypertrophy of the gland in this group was very low. In four guinea-pigs the colloid remained hard; few phagocytes and few mitoses were seen, and the epithelium was of low cuboidal type. In four animals some hypertrophy was noticeable, with beginning softening of the colloid as evidenced by more considerable peripheral vacuolation and a lighter staining of this material. There were a few phagocytes, and some, though on the whole infrequent, mitoses, except in one animal in which the epithelium was higher than in the others but was still cuboidal. In this case we found, contrary to what is usually observed, that although the animal lost weight it showed softer colloid, higher epithelium and more irregularity of the acini than the others. There were few mitoses and few phagocytes.

Group 2 (Dosage: 0.01 Gm.).—Seven guinea-pigs, weighing from 170 to 225 Gm., with an average weight of 198 Gm., were used. Six animals gained on the average 12.6 per cent, while one lost 2 per cent, of the original weight. The average number of mitoses was 885.

In five animals a great deal of hypertrophy was noted, most of the colloid having been absorbed; the acini were irregular; many mitoses were seen, and the epithelium was high cuboidal; the number of phagocytes was moderate except in one specimen in which many were noted. The appearance of the acini varied in the same section from those with slitlike lumens to those with widely dilated lumens containing soft colloid. In the two animals which showed very little hypertrophy the colloid remained, on the whole, hard with some beginning softening; there were few phagocytes and mitoses, and the epithelium was low cuboidal, although a little higher than in the normal guinea-pigs. The acini were regular in these two animals.

Group 3 (Dosage: 0.005 Gm.).—Seven guinea-pigs, weighing from 175 to 225 Gm., with an average weight of 195 Gm., were used. Two lost 3.5 per cent of their original weight; five gained an average of 11 per cent. The average number of mitoses was 585.

In four animals there was a great deal of hypertrophy, with soft colloid, high to medium cuboidal epithelium and irregular acini. The number of phagocytes was not great. In three animals there was only a moderate degree of hypertrophy, much of the colloid being relatively hard, with only beginning softening and vacuolation. The epithelium varied in height from low to medium cuboidal in these three, and the acini remained regular.

GROUP 4 (Dosage: 0.002 Gm.).—Six guinea-pigs, weighing from 185 to 225 Gm., with an average weight of 202 Gm., were used. One lost 5 per cent of its original weight, and five gained 24 per cent. The average number of mitoses was 720.

Five of the animals showed about the same degree of hypertrophy as the animals which received 0.005 Gm. Most of the colloid had been absorbed, and that which remained appeared as pale pink wisps; the epithelium varied from medium to high cuboidal, and the acini were irregular. As was found elsewhere also, in the same piece of the gland and in the same section the colloid sometimes varied from hard to soft, but on the whole there was relatively little hard colloid. There were many mitoses and a number of phagocytes. The acini were not as irregular as those in the animals which received the larger doses. In the one animal which showed only about the same degree of hypertrophy as that found in the controls, the colloid was hard, and few phagocytes and mitoses, low cuboidal epithelium and regular acini were noted.

Summary.—The number of guinea-pigs showing evidence of compensatory hypertrophy of the thyroid gland and the degree of hypertrophy were greater in the groups fed potassium iodide than in the control group. There was more hypertrophy in the animals which received doses of 0.01 Gm. than in those which received smaller doses. However, there was not much difference in the degree of hypertrophy between the animals which received 0.005 Gm. and those which received 0.002 Gm. The number of phagocytes was not prominent, probably because the quantity of iodine administered was in general small. However, in several instances, many phagocytes were observed after the administration of the larger doses. In general, the number of mitoses approximately paralleled the degree of hypertrophy. There is a variegation in the structure after the administration of potassium iodide, for in the same section may be found acini lined with low cuboidal epithelium filled with hard colloid, alternating with acini from which the colloid has been absorbed, resulting in their collapse. This variegation in structure was observed by Loeb [3] in the study of intact thyroid glands in guinea-pigs treated with potassium iodide.

Series B.—Ten doses of potassium iodide were administered during a period of ten days following partial thyroidectomy.

GROUP 1 (Controls).—The greater part of the thyroid gland was removed, but no potassium iodide was administered.

Five guinea-pigs, weighing from 190 to 230 Gm., with an average weight of 206 Gm., were used. The average gain in weight was 7 per cent; three animals

3. Loeb, Leo.: Endocrinology **13**:49, 1929.

gained, and the weight of the other two remained stationary. The average number of mitoses was 175.

In one animal there was considerable hypertrophy. Most of the colloid had been absorbed. Many phagocytes and many mitoses were observed; the epithelium was high cuboidal; the acini were irregular in shape, and many of their lumens were reduced to slits. In the other four guinea-pigs the remnants of the gland showed little hypertrophy. The colloid was hard; there was some peripheral vacuolation in the colloid which took a lighter stain with eosin; the number of mitoses was very small, and the phagocytes were infrequent except in one piece; the epithelium was cuboidal, and the acini were regular. It is of interest to note that the two animals which showed the most marked hypertrophy were the ones which gained the most in weight.

GROUP 2 (Dosage: 0.01 Gm.).—Four guinea-pigs, weighing from 200 to 235 Gm., with an average weight of 209 Gm., were used. One of these animals lost 22.5 per of its original weight; the others showed an average gain of 14 per cent. The average number of mitoses was 555.

There was only a moderate amount of hypertrophy. In two animals the consistency of the colloid ranged between hard and slightly soft; there was some peripheral vacuolation; many phagocytes and mitoses were present, and the epithelium varied in height from medium to high cuboidal. The other two animals showed little if any hypertrophy; the colloid remained hard; very few phagocytes and mitoses were present, and the epithelium was of the low cuboidal type.

GROUP 3 (Dosage: 0.005 Gm.).—Six guinea-pigs, weighing from 195 to 250 Gm., with an average weight of 210 Gm., were used. Five of these on the average gained 11 per cent, while one lost 8 per cent, of the original weight. The average number of mitoses was 300.

In four animals there was moderate hypertrophy with variation of the colloid from hard to soft. In one of these, there were many phagocytes and many mitoses and the epithelium varied from low to high cuboidal. The rest did not show many phagocytes or many mitoses, and the epithelium was from low to medium cuboidal. The animal which showed the greatest hypertrophy gained the most in weight. Two animals showed only a little hypertrophy. The colloid was hard; few phagocytes and mitoses were observed, and the epithelium was low cuboidal. One of these animals had lost in weight.

GROUP 4 (Dosage: 0.002 Gm.).—Four guinea-pigs, weighing from 210 to 240 Gm., with an average weight of 223 Gm., were used. Three gained on the average 2 per cent, while one lost 2 per cent, of the original weight. The average number of mitoses was 30.

There was little hypertrophy in this group, even less than in the control animals. In three animals the colloid remained hard, and the epithelium varied from low to medium cuboidal. In one the colloid was beginning to soften, but the other structural characteristics remained the same as in the other three. The acini were regular, and there were few phagocytes except in the animal in which the colloid was beginning to soften.

Summary.—In this series there was a moderate amount of hypertrophy of the thyroid gland in the animals which received 0.01 and 0.005 Gm. of potassium iodide. The degree of hypertrophy was higher in these animals than in those which received 0.002 Gm., and it was also higher than in the controls. However, the controls showed at least

as much hypertrophy as, and in some cases even more than, did the animals which received the lowest dose.

CONCLUSIONS BASED ON EXPERIMENTS WITH POTASSIUM IODIDE

These experiments confirm the conclusion that potassium iodide increases the degree of compensatory hypertrophy which normally takes place only to a moderate degree when a great part of the thyroid gland has been removed. In addition, it was found that smaller doses than those used in the earlier experiments increase the degree of hypertrophy. Moreover, the intensity of mitotic activity is increased under the influence of potassium iodide, and in general the number of mitoses corresponds to the degree of hypertrophy.

EFFECT OF ANTERIOR LOBE PITUITARY

It has been shown in this laboratory [4] that the feeding of tablets of anterior lobe pituitary prevents compensatory hypertrophy of the thyroid gland of the guinea-pig. On the other hand, Loeb and Bassett [5] found that intraperitoneal injections of either acid or alkaline, subsequently neutralized solution of anterior lobe pituitary extract in daily doses of 1 cc. or even less produce changes in the thyroid gland resembling those found in intense compensatory hypertrophy. The hypertrophy may be noticeable after a single injection (Silberberg [6]), and it increases with the number of injections given until the sixth or seventh day, when an approximate maximum is reached. At the end of the second, third or fourth day, mitotic proliferation is at its height. After this period, the number of mitoses may begin to decrease, while the solution of the colloid and the hypertrophy of the acinus cells still progress. These findings suggested the problem as to the influence of the administration of anterior lobe pituitary on compensatory hypertrophy of the thyroid gland in the guinea-pig following extirpation of the greater part of this organ. In particular was it desired to determine whether as a result of these injections the normal size of the gland would be regained more rapidly.

Three series of experiments were carried out. In the first series (A), the animals were divided into three groups. In one group, one and two-thirds lobes of the thyroid gland were extirpated and 19 cc. of solution of anterior lobe pituitary was given in daily intraperitoneal injections of 1 cc., beginning the day after the operation; the animals were killed on the day following the last injection. Another group received the same doses but the thyroid was left intact. In a third group the same amount of the gland was removed but no solution of

4. Loeb, Leo.: J. M. Research **41**:481, 1920. Loeb, Leo, and Kaplan, E. E.: ibid. **44**:557, 1924. Loeb, Leo.: Am. J. Path. **5**:71, 1929.

5. Loeb, Leo, and Bassett, R. B.: Proc. Soc. Exper. Biol. & Med. **26**:860, 1929; **27**:490, 1930.

6. Silberberg, M.: Proc. Soc. Exper. Biol. & Med. **27**:166, 1929.

anterior lobe pituitary was injected. In the second series (B), the animals were likewise divided into three groups, but they received only ten doses of anterior lobe pituitary, beginning directly after operation. The thyroid glands were examined on the eleventh day following operation. In the third series (C), the guinea-pigs in which the greater part of the thyroid gland had been extirpated received seven doses of anterior lobe pituitary beginning fourteen days following operation. The controls, with intact thyroid glands, were also given injections during the same period.

Series A.—Group 1 (Controls).—Partial thyroidectomy was performed, but solution of anterior lobe pituitary was not injected. Nine guinea-pigs ranging in weight from 175 to 200 Gm., with an average weight of 189 Gm., were used. All of the animals gained weight, the average gain being 30 per cent.

There was only moderate hypertrophy. However, six guinea-pigs showed more evidence of hypertrophy than did the other three. In these six animals, the acini were filled with colloid which was beginning to soften, although it varied from hard to soft. There were infrequent phagocytes and mitoses. The epithelium was a little higher than usual, and the acini were regular in all the animals except one. In the other three guinea-pigs the colloid was still hard; there were few phagocytes, and the epithelium was, on the average, low cuboidal.

Group 2.—One cubic centimeter of solution of anterior lobe pituitary was given daily for nineteen consecutive days following operation. Nine guinea-pigs, ranging in weight from 172 to 200 Gm., with an average weight of 191 Gm., were used. One animal lost 2 per cent of its original weight; the others showed an average gain of 1 per cent.

In all the animals but one, a high degree of hypertrophy was observed. The acini were very irregular, with slitlike lumens, papillae and spurs; the colloid varied from hard to very soft in six of these animals. In the two guinea-pigs which showed the greatest hypertrophy little colloid was left; the epithelium was high columnar, the acini were very irregular, and there were many mitoses. Not many phagocytes were noted in these two animals. In six other guinea-pigs, which showed a little less hypertrophy, there were some mitoses, but the number was apparently not great. One animal showed only moderate hypertrophy, with relatively hard colloid, few phagocytes and mitoses, cuboidal epithelium which was somewhat higher than normal and large distended acini. This animal gained more weight than did any of the others.

Group 3.—Nineteen injections of solution of anterior lobe pituitary were given, but the thyroid gland was left intact. Nine guinea-pigs, ranging in weight from 177 to 235 Gm., with an average weight of 201 Gm., were used. Two animals gained and seven lost weight; the loss in weight was, on the average, 4 per cent.

All these guinea-pigs showed striking hypertrophy. In all but two by far the greater part of the colloid had been absorbed and only a few pale shreds remained; the epithelium was high columnar, the acini were irregular and showed papillae and spurs, and the lumens were often reduced to slits. In two animals, similar changes were noted but a good deal of colloid was left. In one of the two, phagocytes were frequent. Many mitoses were observed in all the guinea-pigs except the last two mentioned.

Summary.—Hypertrophy of the thyroid gland of the guinea-pig was produced in the intact gland as well as in the remnants of the partially extirpated gland as a result of the administration of anterior lobe pituitary. On the whole, the degree of hypertrophy in the parts of the

glands remaining after operation not only was no greater than that observed in the intact glands, but was somewhat less. This result may perhaps be explained by the fact that in the peripheral acini of the thyroid gland hypertrophy is always less marked than in the central parts. If a great part of the gland is extirpated and only a small remnant is left, the circumference of the small piece is relatively more preponderant than it is in the intact gland. Thus the hypertrophy may be diminished in a relatively greater number of acini as a result of the partial extirpation.

Furthermore, it was found that it is not possible by means of injections of solution of anterior lobe pituitary to accelerate the restitution of the remnant to the normal size. There was no appreciable difference in size between the remnants of the thyroid glands in the guinea-pigs which had received the extract following operation and in those which had not. If, then, one finds as a result of the injection of solution of anterior lobe pituitary, a marked increase in the size of the cells and in the number of mitoses as compared with those of the control animals, it must be due to the fact that the hypertrophy and hyperplasia produced by anterior lobe pituitary change the structure of the remaining portion of the gland without an actual expansive growth becoming manifest. One must assume that the spaces where formerly colloid was present are occupied by cellular elements.

Series B.—GROUP 1 (Controls).—Partial thyroidectomy was performed, but the animals did not receive anterior lobe pituitary. Seven guinea-pigs, ranging in weight from 195 to 240 Gm., with an average weight of 216 Gm., were used. One animal lost 2 per cent of its original weight; the remaining six gained, on the average, 11 per cent.

In three animals there was moderate hypertrophy, with softening and vacuolation of the colloid, slightly enlarged epithelium and regularly shaped acini. Many phagocytes appeared in one of the animals, which showed the greatest softening of the colloid. Some mitoses were noted in each animal, and they were frequent in one. Four animals showed only slight hypertrophy, with hard colloid, few phagocytes and mitoses, only slightly enlarged epithelium and regular acini.

GROUP 2.—One cubic centimeter of solution of anterior lobe pituitary was given daily for ten consecutive days following operation. Seven guinea-pigs, ranging in weight from 210 to 265 Gm., with an average weight of 225 Gm., were used. Three animals gained and four lost weight, the average loss being 2 per cent.

Three animals showed a great deal of hypertrophy, with high cuboidal epithelium, irregular acini with slits and spurs and greatly softened colloid. The other four showed a little less hypertrophy, with more regular acini, medium cuboidal epithelium and more remaining colloid. The number of phagocytes and mitoses was not striking in any of the animals.

GROUP 3.—Ten cubic centimeters of solution of anterior lobe pituitary was given, but the thyroid gland was left intact. Seven guinea-pigs, ranging in weight from 190 to 210 Gm., were used. One of these animals gained 8 per cent of its original weight, while six lost, on the average, 6 per cent.

All the animals showed a high degree of hypertrophy. The acini were irregular, and many slits and papillae were visible; the epithelium was columnar, and the colloid had been almost entirely absorbed in all but two animals. In these two the epithelium was cuboidal, although higher than in the acini of normal guinea-pigs, the acini were fairly regular and the colloid was soft. In the guinea-pig which showed the greatest hypertrophy there were many phagocytes and many mitoses. In the others there were some phagocytes and mitoses, but their number was not great.

Summary.—The degree of hypertrophy in this series was not as high as in the preceding one, but, as in the former series, the animals which received anterior lobe pituitary without operation showed a greater degree of hypertrophy of the thyroid gland and lost more weight than the animals which received the extract after operation. The control animals, which did not receive anterior lobe pituitary after operation, showed the least hypertrophy. It should be noted, however, that this series of experiments was carried out during April and May, while the other two series were carried out during the colder months of the year. This difference may possibly account for the fact that less hypertrophy was noted.

Series C.—Seven cubic centimeters of solution of anterior lobe pituitary was given, beginning fourteen days after operation. The animals were killed on the day following the last injection. In the first group, which received 7 cc. of solution, the thyroid gland was left intact; in the second group, a great part of the gland was removed, but no injections were given, and in the third group the injections were given after a great part of the gland had been removed.

Group 1 (Controls).—The thyroid gland was partially extirpated, but the animals received no anterior lobe pituitary. Ten guinea-pigs, ranging in weight from 245 to 290 Gm., with an average weight of 263 Gm., were used. All of the animals gained in weight, the average gain being 32 per cent.

Nine guinea-pigs showed very slight hypertrophy of the acinar epithelium with regular acini; the colloid showed a little softening in all but two, in which it remained hard. In one animal there was more hypertrophy; a great part of the colloid had been absorbed; the epithelium was higher, and the acini were irregular, the lumens of many being reduced to slits. As a rule phagocytes as well as mitoses were not frequent.

Group 2.—Seven cubic centimeters of solution of anterior lobe pituitary was given following partial thyroidectomy. Nine guinea-pigs, ranging in weight from 250 to 300 Gm., with an average weight of 266 Gm., were used. All of the animals gained weight, the average gain being 26 per cent.

Seven guinea-pigs showed a high degree of hypertrophy. The epithelium was columnar, and the acini were very irregular with many slitlike lumens and papillary projections. Most of the colloid had been absorbed, and there was a moderate number of mitoses. There were some phagocytes in all these animals. Two animals showed moderate hypertrophy, with medium cuboidal epithelium; the colloid was for the most part soft, but some hard colloid was left and the irregularity of the acini was less marked. However, in one of these two animals many phagocytes and mitoses were found.

GROUP 3.—Seven cubic centimeters of solution of anterior lobe pituitary was given to animals in which the thyroid gland was intact. Four guinea-pigs, ranging in weight from 275 to 305 Gm., with an average weight of 263 Gm., were used. All of the animals lost weight, the average loss being 9 per cent.

The degree of hypertrophy in three animals was about the same as in the second group of this series, but the acini were not so irregular. The epithelium was columnar, and the colloid either had been absorbed entirely or was softened. In one animal the acini were regular and some hard colloid was left, but the epithelium was high and there were many mitoses.

Summary.—In this series the degree of hypertrophy in the thyroidectomized animals which received anterior lobe pituitary was very high and corresponded in intensity to that observed in the animals which received the extract but were not operated on. As had been noted in the preceding series, the hypertrophy was much greater in the guinea-pigs which had received anterior lobe pituitary than in those in which a part of the gland had been extirpated but which did not receive the extract. On the whole, the partially thyroidectomized animals in this series showed much greater compensatory hypertrophy than did those in the preceding series, which were given 10 cc. of solution of anterior lobe pituitary. This difference may perhaps be due to the fact that the experiment in which 10 cc. was administered was carried out during the warmer season; this interpretation agrees with previous findings of Loeb concerning the seasonal variations in the intensity of compensatory hypertrophy. However, the fact that in this series the injections were begun only fourteen days following the operation, while in the preceding series they were started directly following the operation, must also be considered. The size of the remnants of the thyroid glands was about the same in the animals which did and in those which did not receive anterior lobe pituitary. The increase in hypertrophy, therefore, does not necessarily lead to a noticeable increase in the volume of the remnant, but leads in the main to an increase in the parenchyma at the expense of the colloid, which is largely absorbed or liquefied.

GENERAL CONCLUSIONS

The hypertrophy of the thyroid gland caused in guinea-pigs by the injection of sufficient quantities of solution of anterior lobe pituitary is, on the average, much greater than the hypertrophy caused in the remaining portions of the gland by the removal of one whole lobe and the greater part of the second lobe.

While each of the two processes studied, namely partial thyroidectomy and the injection of anterior lobe pituitary, tends to cause hypertrophy of the thyroid gland, their combination does not lead to a summation of the separate effects. On the contrary, in some cases, after removal of the greater portion of the thyroid gland the hypertro-

phy of the remaining part caused by the injection of anterior lobe pituitary may be less than the hypertrophy elicited in an intact thyroid gland.

If one compares the effect of potassium iodide with that of anterior lobe pituitary on compensatory hypertrophy following extirpation of the greater part of the thyroid gland in guinea-pigs one finds that these two substances behave differently: While potassium iodide distinctly intensifies compensatory hypertrophy following partial extirpation of the thyroid gland, no summation of hypertrophic effects is produced by the administration of anterior lobe pituitary and partial thyroidectomy; on the contrary, under certain conditions there may be a diminution of the hypertrophy caused by anterior lobe pituitary as a result of previous extirpation of the greater part of the gland.

PEROXIDASE ACTIVITY OF HEMATIN

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It has long been known that blood will catalyze the decomposition of hydrogen dioxide. When benzidine, guaiac and other aromatic chromogens are present these are oxidized to blue-colored compounds. This is known as peroxidase activity. The benzidine test for blood is a practical application of the principle involved.

The present report is an outgrowth of a study of the immunologic reactions of hemoglobin and particularly globin, the protein part of the hemoglobin molecule, and the rôle that it plays in these reactions. Hektoen and Schulhof [1] found that when oxyhemoglobin was changed to methemoglobin, sulphemoglobin or carbon monoxide hemoglobin [2] the antigenic titer remained the same as the original compound. In my experience, too, oxyhemoglobin antiserum reacts with methemoglobin in the same dilution as oxyhemoglobin, the original antigen. Moreover, hematin itself does not form precipitins with hemoglobin antiserum. There is little doubt, therefore, that the antigenic properties of hemoglobin reside in the globin part of the molecule.

It is a well known fact that when hemoglobin is treated with acid it splits into globin and acid hematin. The separation of acid hematin from globin is difficult, and unless conditions of temperature and acidity are closely controlled the product formed is so completely denatured (insoluble in neutral solvents) that it is rendered useless for immunologic studies. According to the literature,[3] the preparation of native or undenatured globin from hemoglobin is an accomplished fact. Despite this, I have been unable to prepare such a protein free from hemoglobin or hemoglobin-reacting substances. In an attempt to use the titer of an antiserum for hemoglobin as a criterion for the purity of globin preparations, the theoretical question arose: Is it not possible, when hemo-

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1. Hektoen, L., and Schulhof, K.: J. Infect. Dis. **41**: 476, 1927.

2. Boor, A. K., and Hektoen, L.: J. Infect. Dis. **46**: 1, 1930.

3. A review of the literature on globin up to 1930 is given by Anson, M. L., and Mirsky, A. E.: J. Gen. Physiol. **13**: 469, 1930. Later publications are those of Hamsik, A.: Ztschr. f. physiol. Chem. **187**: 229, 1930; Troensegaard, N.: ibid. **199**: 129, 1931; Schenck, E. G.: Arch. f. exper. Path. u. Pharmakol. **150**: 160, 1930.

globin is used as an antigen, that some of it is split in vivo with the consequent production of two precipitins; one, for the hemoglobin molecule as a unit, the other, for globin alone? If this is true the hemoglobin antiserum will give no information as to the purity of the globin preparation in question. All globin preparations reacted in low dilutions, 1 part in 1,200 to 1 part in 2,000, with hemoglobin antiserums.

With regard to the problem at hand, it was also noted that these globin preparations showed distinct peroxidase activity; hence it became rather pertinent to inquire into the chemical basis for the benzidine test for blood.

In preliminary tests it was observed that hematin shows a strong peroxidase activity. To obtain a quantitative estimate of this activity as compared with whole blood, it was necessary to prepare pure hematin. Nencke and Zaleski [4] have described a satisfactory method for the preparation of acid hematin. Elvehjem's [5] modification of the older methods was the one used in this study.

METHOD

If the whole blood is added drop by drop to a 95 per cent solution of hot acetic acid containing a trace of sodium chloride, crystalline hematin hydrochloride is formed on cooling. The crystals are readily separated from the mother liquor by filtration or by centrifugation, washed with cold dilute acid and alcohol, and dried. To insure absolute purity, the first product was recrystallized according to the method of Schalfejeff as described by Nencke and Zaleski.[4] Equal quantities of hemin and quinine (base) were dissolved in warm chloroform, and this solution was slowly added to hot acetic acid. As in the original preparation, constant stirring and the presence of sodium chloride are necessary. The crystals thus obtained gave on analysis for iron, figures which agreed with the formula $C_{34}H_{33}O_4N_4FeCl$ for hemin. The theoretical figure for iron was 8.59 per cent; the average of analyses, 8.54 per cent. The crystalline form and appearance of hemin did not change on recrystallization.

A known weight of recrystallized hemin was dissolved in dilute sodium carbonate, and successive dilutions of 1 part in 10, 1 part in 100, etc., were made. At the same time, samples of fresh blood were obtained and hemoglobin determined on the basis of iron. Knowing the iron content of hemin and that of the samples of blood, the peroxidase activity of each was compared at successive dilutions on the basis of the same iron content. This was carried out in a porcelain spot plate, 1 drop of benzidine in glacial acetic acid, 1 drop of the solution to be tested and 1 drop of 3 per cent solution of hydrogen dioxide being used. In every trial it was observed that the peroxidase activity of hematin was equal to that of blood. In dilutions of 1 part in 100,000, the hematin solution gave distinctly more positive reactions. The limit of the reaction is about 1 part in 200,000 or slightly higher.

These observations with respect to the chemical basis for the blood-benzidine reaction are by no means original with me. After making

4. Nencke and Zaleski: Ztschr. f. physiol. Chem. **30**:384, 1900.
5. Elvehjem, C. A.: J. Biol. Chem. **93**:203, 1931.

preliminary tests, it was found that Wu,[6] in 1922, not only reported the peroxidase activity of hematin, but also described a quantitative method for the determination of hemoglobin by using this activity of hematin as a standard of comparison. More recently, modifications of Wu's method were reported by Bing and Baker.[7] Improvements in the qualitative application of the test were described by Ingham.[8] As the test is applied to acid-ether extracts of gastric contents, urine, feces and other biologic materials it is a test for hematin and not for hemoglobin. Moreover, native globin free from hemoglobin and hematin will in all probability not give the test.

CONCLUSION

It appears that hematin is responsible for the peroxidase activity of blood.

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6. Wu, H.: J. Biochem. **2**: 181 and 189, 1922.

7. Bing, F. C., and Baker, R. W.: J. Biol. Chem. **92**: 589, 1931.

8. Ingham, J.: Biochem. J. **26**:1124, 1932. McFarlane, W. D., and Hamilton, R. C. M.: ibid. **26**: 1050, 1932.

Laboratory Methods and Technical Notes

A SIMPLIFICATION OF THE COOLED KNIFE METHOD (SCHULTZ-BRAUNS) FOR OBTAINING FROZEN SECTIONS

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In 1931, Schultz-Brauns [1] described a modification of the method for obtaining frozen sections for which he claimed certain advantages over the commonly used technic. He developed an apparatus with which the knife could be cooled below the freezing point (approximately — 5 C.). A second tubing was attached to the carbon dioxide tank and connected with a special outlet which was fixed between the holders of the knife. By the opening of a valve, carbon dioxide could be sprayed on the knife which thereby cooled to the proper temperature. Sections cut with the cooled knife were taken from the knife directly to the slide. Schultz-Brauns pointed out that even very friable tissue, such as is found not infrequently in tumors and necroses, could be cut and attached to the slide without losses or other difficulties. The contents of glands and cysts were not dislocated or lost when this method was used, while this often occurred in sections cut by the common technic. Fixed and unfixed tissues could be cut with equal ease. The stained sections compared well in quality with those prepared with the paraffin method. He found his technic, moreover, useful in the preparation of sections for ashing, because the sections cut with the cooled knife did not come into contact with any agent (fixation and dehydration fluids) which was apt to change the amount and distribution of the mineral constituents of the cells.

TECHNIC

During recent investigations which necessitated the use of frozen sections, a simple apparatus was developed which seems to work just as well as the somewhat complicated and specially constructed arrangement of Schultz-Brauns. This can be built with practically no cost or special technical skill, and it has the advantage of keeping the knife at the proper temperature for about from five to ten minutes without any attention, while the apparatus used by Schultz-Brauns requires a spraying of the knife at intervals of one minute.

A rectangular trough was constructed of thin tinned plate which could be cut with wire shears. It measured 3 by 1 by 1 inch (7.6 by 2.5 by 2.5 cm.). It was just large enough so it could be squeezed between, and be retained by, the two holders of the microtome knife. One half of the bottom of the trough was then cut out. When the trough was put into place, the open part of the bottom was so placed that it rested on the back half of the knife, while the closed portion of the

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1. Schultz-Brauns, O.: Centralbl. f. allg. Path. u. path. Anat. **50**:273, 1931; Klin. Wchnschr. **10**:113, 1931.

bottom of the trough extended beyond the knife backward. The trough was then packed with carbon dioxide snow, or with "dry ice" when it was obtainable. Through the direct contact with the carbon dioxide the knife was cooled to the proper temperature. The piece of tissue to be cut was then placed on the peripheral part of the freezing platform in such a way that the knife would have to pass over almost the entire platform before hitting the tissue block. This arrangement is important for the subsequent easy removal of the section from the knife. After the tissue was properly frozen, the knife was carried through the tissue block in such a way that the section remained attached to the block with a narrow margin. The rolled up, still frozen section was flattened out on the cold knife with the help of a fine, long-haired brush. The temperature of the knife did not allow a thawing of the section. A slide was then brought into contact with the section, which became readily attached to the warm slide and stuck to it. The section was then ready for further treatment or direct examination.

It was of advantage to place sections from unfixed material (after mounting them on slides) in 95 per cent alcohol for a few seconds before putting them into hematoxylin, as thereby more clearly stained pictures were obtained and no disturbing precipitations of dye resulted. After some experience with the technic had been obtained, serial sections could be cut. The stained sections were in many respects as good as paraffin sections and were occasionally even better than these, when the tissue contained cells of rather delicate structure, such as are sometimes present in certain tumors, where the usual preparation for paraffin sections resulted in more or less marked distortions owing to excessive shrinkage.

COMMENT

The claims made by Schultz-Brauns for his method of obtaining frozen sections with the cooled knife are confirmed. The method is simple and quick, and gives much better results than those obtained with the common technic, especially when unfixed tissues are used. It is therefore particularly well suited to the preparation of quick frozen sections from biopsy. It represents the method of choice for sections to be ashed, as it is the only method which allows relatively reliable comparative qualitative and quantitative studies of the mineral content of cells. It may also be applied with advantage to the investigation of vitally stained tissues or of colored deposits and precipitations which are soluble in water or the agents used in the preparation of paraffin sections. With the simple and inexpensive apparatus described, the method of obtaining frozen sections with the cooled knife can be recommended for general use in place of the commonly used technic.

General Review

HODGKIN'S DISEASE

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(Concluded from page 562)

CHEMISTRY

The chemical aspects of Hodgkin's disease are little known. The following data are taken from isolated sources in the hope of building up this phase of the subject. Reports based on the leukemias and similar conditions are included in order to show similarities or differences. Chemical studies in this field are necessarily greatly affected by a number of variables, such as the point of localization, the special organs affected and the concurrent disease processes.

Starlinger and Winands found that in lymphogranuloma the blood shows a normal total protein content, an absolute and relative increase in fibrinogen, a moderate absolute and relative increase in globulin and a significant absolute and relative decrease in albumin. In the cachexia of lymphogranulomatosis, the protein content shows a progressive decrease, and the globulin returns to a normal value, with the relative increase preserved. Under favorable irradiation the protein content is normal; globulin shows a high normal value; albumin, a low normal value, and fibrinogen a moderate relative and absolute increase. The authors gave an extensive review of the literature.

Studies on blood cholesterol are more numerous. Currie, in a case of lymphogranuloma, found a value of 250 mg. per hundred cubic centimeters indicating a slight decrease. Freifield's case showed a content of 136 mg. Luden observed a case of Hodgkin's disease for two years, making determinations of cholesterol at weekly intervals (the condition later became generalized lymphosarcoma, according to him). After radium treatment, the pure cholesterol was decreased, and the split cholesterol increased. After roentgen treatment this proportion was reversed, pure cholesterol being increased and split cholesterol decreased. Luden remarked that when the pure cholesterol was increased, together with reduction of split cholesterol, new nodal enlargements would be found. This change always seemed to herald a recurrence. In another

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paper, Luden stated that a diet which increases the blood cholesterol also causes lymphopenia, and that the same phenomenon occurs in persons predisposed to carcinoma. Sanders, working along similar lines, found that a diet leading to elevation in the blood cholesterol will produce an associated increase in polymorphonuclears with lymphopenia, and vice versa. Stenhouse, after a study of tropical hydrocele, expressed the belief that cholesterol has something to do with the production of lesions associated with obstruction of lymph channels. Generally speaking, the location of the lesion in the lymphogranulomatous process, (e. g., a close anatomic relationship to the liver or pancreas) would conceivably have considerable influence on the amount of cholesterol. Twort estimated the blood lipase, finding a decrease in lymphogranuloma and in certain diseases of the blood, which was not differential. Happold and Taylor estimated the lipase content of several organs in tuberculosis, finding a reduction in the liver and the spleen, and a value close to normal in the lungs. Twort found that in the liver the amount of lipase varied according to the amount of remaining parenchyma, and that the amount was not specific according to the disease present. Susman and Happold came to the conclusions (in connection with tuberculosis) that proliferation of the functioning cells of an organ causes an increase in its lipolytic activity, that necrosis establishes a decrease according to the extent of the lesion, and that proliferation of the stroma also causes a decrease, but less than that produced by necrosis. They stated finally that the reaction varies according to the damage to the cells and not according to the disease.

The basal metabolic rate in lymphogranulomatosis and in leukemia has been studied by Holbøll. He found the rate generally increased; when it was lowered during treatment the general condition was improved. A continued high value signified a poor prognosis. The rise is ascribed to some of the accompanying symptoms, especially the emaciation. Krantz, in 30 cases of lymphoblastoma, found that the basal metabolic rate was elevated but that it could be reduced by proper irradiation. Leukopenia is not a contraindication to irradiation in cases in which the basal metabolic rate is increased. The basal metabolic rate is valuable in the determination of therapy and of prognosis. Baldridge and Awe often found it elevated in all types of "lymphoma."

Ordway found that radium treatment of an enlarged spleen in leukemia increased the proteins, total nitrogen, urea, ammonia and phosphates of the urine. The urinary changes are due partly to products derived from autolysis of bone marrow under the influence of irradiation.

Ehrlich's diazo-reaction was reported to be positive in two thirds of cases by Borsutzky, a finding corroborated by several other writers.

Rabinowitch stated that a diazo-reaction is not found in any condition unassociated with severe renal damage. Andrewes' modification of Hewitt's test was used, and the work was done in connection with uremia. Isaacs stated that the diazo-reaction is often positive in lymphogranuloma without visible enlargement of the lymph nodes (Ziegler's larval or typhoid form).

Galloway reported the finding of Bence-Jones protein in lymphogranuloma. The relationship between this substance and renal insufficiency was discussed by Bannick and Greene, who found them frequently associated. Perhaps the appearance of this protein is the result of renal damage, and not as intimately related to involvement of the bone marrow as is usually stated. Schmidt reported an increase in the amino-acids of the blood in leukemia, especially of the myelogenous variety.

Urechia and Goia called attention to the value of examination of the spinal fluid. The colloidal gold test gave incomplete precipitation in tubes 2 and 3, as is common in tumors, but not in meningitis, in which the curve is longer and deviated to the right. This was confirmed in some cases by Mathieu, and by Thomas and Paix, who found an increase in albumin and a prolonged benzoin curve. Urechia and Goia's case showed involvement of the dura but little involvement of the pia arachnoid at autopsy, thus confirming their findings.

Vasiliu and Goia, in 3 cases of abdominal Hodgkin's disease, found that the gastric juice always showed hypo-acidity or anachlorhydria. Brack, in a case in which pruritus was present, found that a test of alimentary hemoclasis (ingestion of 200 cc. of milk) produced a marked reaction, the calcium-potassium quotient showing a definite fall. This reaction he interpreted as indicating a parasympathicotonic disturbance.

IMMUNOLOGY

De Negri and Mieremet tried to obtain fixation of complement in 2 cases, using Corynebacterium granulomatis-maligni as antigen. From similar studies Olitsky found that C. hodgkini is a distinct diphtheroid organism, separable from Corynebacterium xerosis and Corynebacterium hoffmanii. Ayrosa made the complement-fixation test with a diphtheroid organism resembling C. hodgkini, obtaining a positive reaction in a case of Hodgkin's disease and negative reactions in cases of other lymphadenopathies.

Rosenthal used the Widal test to differentiate the larval or typhoid form of lymphogranuloma from typhoid and paratyphosus A and B, and cited a case. Twort, working with agglutination, precipitation and other test tube reactions, could demonstrate no specific antigens or antibodies in patients with Hodgkin's disease. He also found them to be reaction-

less to tuberculin, vaccines and specific antiserums (prepared from rabbits inoculated with lymphogranulomatous tissues and filtrates). This is contrary to Fraenkel and Much's results. He further attempted to produce specific antibodies in animals by the administration of emulsions of lymphogranulomatous, leukemic and normal lymph nodes. Some success was obtained in producing cyto-agglutinins. It is interesting to note that co-agglutinins for leukemic and normal tissue emulsions were rarely absent, and that they could be removed by adsorption, the specific agglutinins remaining. All the agglutinins were destroyed after one hour at 60 C. Attempts by Grumbach to agglutinate the bacillus which he isolated from the blood stream by culture were not successful.

MacNalty made estimations of the opsonic index, with normal findings (0.8 to 1.2). In a case of tuberculous adenitis with recurrent fever, the index was 1.37 after massage of the enlarged glands. He suggested the value of the opsonic index in differential diagnosis.

Fox and Farley attempted skin tests, using comminuted lymphogranulomatous tissue; the results were negative not only in Hodgkin's disease but in sarcoma (1 case) and in aleukemic leukemia (1 case). Hanrahan also tried skin tests.

Stewart and Doan investigated the phosphatid fraction of the lipoids of the tubercle bacillus as an antigen, and in the course of the work studied several cases of Hodgkin's disease. The serum of tuberculous patients frequently showed abilty to precipitate the tuberculophosphatid in high titer. In 9 cases of Hodgkin's disease "the presence of free phosphatid-antigen was suggested in tests with antisera for avian phosphatid, four of the cases also giving a positive precipitin reaction with anti-human tuberculo-phosphatid serum." This antiserum was prepared from rabbits, and the reactions were obtained in the patients' serum. It is also to be noted that in 24 cases of verified Hodgkin's disease precipitation with human tuberculophosphatid occurred in various titers as follows: 160—all cases; 320—23 of 24; 640—20 of 24; 1280—8 of 24; 2,000—2 of 24. These results are striking, especially when compared with the results obtained in other diseases clinically and anatomically resembling Hodgkin's disease, in none of which, with the exception of 3 cases of pseudoleukemia, were such numerous positive reactions found.

CLASSIFICATIONS AND RELATIONSHIPS

Simonds, in his review, considered the relation of Hodgkin's disease to other diseases of the lymph nodes and the possibility of its sarcomatous transformation. His emphasis on the ignorance of etiologic factors in these diseases is to the point, for certainly no fully acceptable

genetic classification can be made until an advance in the knowledge of the etiology has been accomplished. He logically suggested the adoption of Ewing's view that clear histologic distinctions be maintained between the various forms of enlargement of the lymph nodes, in order not to retard the discovery of etiologic factors. Because of the uncertain state in which this matter of relationships and classification of diseases affecting lymph nodes and the hematopoietic system is found, this review will be limited to a presentation of the following outstanding classifications, with supplementary citations from the literature on general relationships.

Baldridge and Awe—

Lymphoma

1. Sclerosing type (Hodgkin's disease)
2. Endothelial type (lympho-epithelioma)
3. Lymphoblastic type (lymphosarcoma)
4. Lymphocytic type
   (*a*) With leukemia (lymphatic or lymphocytic leukemia)
   (*b*) Without leukemia (pseudoleukemia or aleukemic leukemia)

Klein—

Lymphoblastoma (occurring in the skin)

1. Leukemia
2. Lymphosarcoma
3. Granuloma fungoides
4. Hodgkin's disease
5. Sternberg's leukosarcoma
6. Kaposi's lymphoderma perniciosa

Bunting and Yates—

I. Hodgkin's disease; terminal pictures
   1. Almost complete sclerosis (typical fibroblastic proliferation)
   2. Sarcomatoid picture (atypical fibroblastic proliferation)
   3. Endotheliomatoid picture (atypical endothelial proliferation, usually with marked giant cell formation)

II. Lymphoblastic group
   Large cell proliferation infiltrating the whole gland, apparently due to proliferation of the large cells of the germinal centers; may become fibrous with giant cells

III. Lymphocytic group
   Diffuse proliferation of small lymphocytes with very early loss of architecture; scattered lymphoblasts and atypical endothelioid cells may occur

(Transition forms between any of these groups may occur)

Hazen—

I. Lymphomatoses
   1. Leukemic (lymphatic leukemia)
   2. Aleukemic (Hodgkin's disease and mycosis fungoides)

II. Myelomatoses
   1. Leukemic (splenomyelogenous leukemia)
   2. Aleukemic (multiple myeloma)

III. Lymphosarcomas
1. Leukemic (leukosarcoma)
2. Aleukemic (lymphosarcoma)
(Mixed types theoretically possible; leukemic types may have aleukemic stages, and vice versa)

Minot and Isaacs—

Lymphoblastoma (malignant lymphoma)
1. Lymphatic leukemia (lymphocytic and lymphoblastic)
2. Aleukemic lymphatic leukemia
3. Pseudoleukemia (aleukemic lymphadenosis)
4. Lymphocytoma
5. Hodgkin's disease (lymphogranuloma)
6. Lymphadenia
7. Lymphomatosis
8. Lymphosarcoma
9. Round cell sarcoma
10. Leukosarcoma
11. Lymphadenosarcoma
12. Banti's disease
13. Chloroma
14. Mikulicz's disease

Pappenheim (according to Dickinson and Lwow)—Diseases of the hematopoietic system

I. Generalized leukocytomatosis (all the leukemias)
1. Lymphadenosis.
(*a*) With leukemic blood
(*b*) Without leukemic blood
2. Myelosis
(*a*) With leukemic blood
(*b*) Without leukemic blood

II. Generalized granulomatosis, including Hodgkin's disease and all generalized inflammatory diseases of the lymph nodes, such as tuberculosis, syphilis and Banti's disease

Rieux (adding to Pappenheim's classification)—

I. Lymphadenosis
(*a*) With or without leukemic blood
1. Benign or malignant
2. Generalized or localized

II. Myelosis
(*a*) With or without leukemic blood
1. Benign or malignant
2. Generalized or localized

(All possible combinations may be met with; in designating the disease, the terminology just given is used; for example, lymphatic leukemia becomes "benign generalized leukemic lymphadenosis," and lymphosarcoma is called "localized malignant aleukemic lymphadenosis")

Sternberg—

Pseudoleukemia, to include
1. Lymphosarcoma
2. Lymphogranuloma

3. Plasmoma
4. Diseases with hyperplasia of lymphoid tissue without leukemic blood

Ewing—

Tumors of Lymphoid Tissue

Origin	Anatomic Type	Clinical Type
Lymphocytes	Lymphocytoma	Simple lymphoma Tuberculous lymphoma Lymphatic leukemia Pseudoleukemia Malignant lymphocytoma
Reticulum cells	Large round cell hyperplasia or neoplasia	Granuloma malignum Myeloid leukemia Hodgkin's sarcoma Large cell lymphosarcoma
Endothelial cells	Endothelial hyperplasia or neoplasia	Endothelial hyperplasia of tuberculosis, etc. Endothelioma

Ceelen and Rabinowitch—

Hematoblastoses

1. Leukemic
2. Aleukemic
   (*a*) Hyperplastic (such as myeloma and true sarcomas)
   (*b*) Chronic inflammatory granulation tissue (such as lymphogranuloma)
   (*c*) Tuberculosis and syphilis

Fox and Farley—

Lymph Gland Enlargements

Character of Pathologic Change	Clinical Character	Pathologic Group	No.	Specific Varieties	Association
Hyperplasia	Benign	Lymphoma	1	Lymphoma, status lymphaticus	
			2	Lymphadenoma	
			3	Glandular fever and acute leukemia	
	Malignant	Leukemia	4	Leukemia	With 5
			5	Aleukemia or generalized lymphomatosis	With 4 or 6
		Neoplasm	6	Leukosarcoma	With 5
			7	Lymphosarcoma	With 10 and 11
			8	Reticular sarcoma	
			9	Endothelioma	
Neo-inflammatory	Malignant	Lymphogranuloma	10	Cellular hyperplasia	With 7 or 8
			11	Fibrosis	With 7 or 8
Inflammatory	Benign	Adenitis	12	Simple	
			13	Purulent	
			14	Tuberculous	With 11
			15	Syphilitic	

Goormaghtigh—

Lymphoid tumors (classified for clinical practice)

1. Granuloma, specific or nonspecific
2. Inflammatory hyperplasia, localized or general
3. Benign tumors: lymphoma

4. Malignant tumors:
   Type 1—lymphatic leukemia
   Type 2—(*a*) lymphosarcoma
   (*b*) reticulo-endothelioma or reticulo-endotheliosarcoma
   Between groups 1 and 4 may be placed lymphogranuloma.

The question of a possible relationship of Hodgkin's disease to sarcoma may be conveniently stated as follows (in an affirmative sense):

1. Hodgkin's disease is a form of sarcoma, beginning and ending as such, and having its origin in one of several types of cells, according to the observer—endothelial cells, reticulum cells, reticulo-endothelial cells, myeloblasts, lymphoblasts or megakaryoblasts.

2. It exists as a specific granuloma, which in some cases may be transformed into sarcoma, and especially into lymphosarcoma (Sternberg; Mueller; Levin).

3. Lymphosarcoma and Hodgkin's disease may exist together in the same patient (Levin; Miller).

4. Many cases of "Hodgkin's sarcoma" originate in the epithelial reticulum cells of the thymus (Ewing).

5. Hodgkin's disease at times exhibits the quality of invasion, a characteristic of sarcoma (Chiari; Karsner; Yamasaki; Yates and Bunting).

6. Invasion is not entirely characteristic of malignancy, but has been observed in known granulomatous tissue (Simonds; Chiari).

7. While the differentiation of lymphosarcoma and Hodgkin's disease may be difficult in some stages, Hodgkin's disease sooner or later assumes its characteristic picture (Symmers).

8. The cells found in Hodgkin's disease, lymphosarcoma and lymphatic leukemia closely resemble those of chronic inflammatory lymph node processes, the only difference being in the presence of an increased number of immature cells with larger nucleoli. Without studies of the blood, it seems to be impossible to differentiate the nodes of lymphatic leukemia from those of atypical Hodgkin's disease or lymphosarcoma. It is probable that these three states have a common neoplastic cellular origin (MacCarty).

9. Hodgkin's disease is a granulomatous process and bears no relation to sarcoma (MacCallum).

Yamasaki, Dietrich, Gibbons, Coley, Chiari and Oliver have all expressed their belief that Hodgkin's disease is genetically related to sarcoma. Oliver offered arguments in favor of such a relationship between Hodgkin's disease, lymphosarcoma and endothelioma. Webster studied a series of 123 cases of lymphosarcoma, lymphatic leukemia, leukosarcoma and Hodgkin's disease, and concluded that while the first

three diseases may be considered as different manifestations of the same condition, Hodgkin's disease is probably a pathologic entity. Warthin was convinced of the relationship between Hodgkin's disease, the various forms of sarcomatous Hodgkin's disease, reticular sarcomas of the lymph nodes and various aleukemic and leukemic lymphoid tumors. These he strongly believed to form a distinct class of neoplasms, basing his opinion on his many years of observation of lymphoid tumors. Levin believed Mikulicz's disease to be a form of Hodgkin's disease, while Ziegler believed Mikulicz's disease to be only a granulomatous involvement of lymph nodes. Reiche reported an interesting case of this disease which presented some resemblance to lymphogranuloma, enlarged nodes, splenomegaly and leukopenia. Külbs also discussed this question.

Fox and Farley discussed the relationship between aleukemic leukemia, pseudoleukemia and malignant granuloma and pointed out the histologic and clinical differences. Herriman and Rahte cited a case of thymoma which clinically resembled Hodgkin's disease, and Helvestine called attention to the close histologic resemblance of some thymomas to Hodgkin's disease. Ewing's description of lympho-epithelioma appears to be somewhat similar to the classic picture of Hodgkin's disease. His views on Hodgkin's sarcoma and thymoma are well known. Ceresoli reported the occurrence of lymphogranuloma and lymphangio-endothelioma in the same patient, and of lymphogranuloma with Hodgkin's sarcoma and spindle cell sarcoma.

Banti recognized that splenic anemia may be accompanied by enlargement of the lymph nodes, and that the changes in the spleen in Banti's disease and pseudoleukemia splenolymphatica are similar. He thought it possible to regard Banti's disease as Hodgkin's disease of the spleen. This connection was further emphasized by Yates, Bunting and Kristjanson, on the basis that a diphtheroid organism obtained from the spleen in 2 cases of Banti's disease, when injected into animals, reproduced the lesion.

Regarding true Hodgkin's disease and Hodgkin's sarcoma, Barron held that the sarcoma is engrafted on the inflammatory tissue of Hodgkin's disease and is not to be regarded as an integral part of the disease. Symmers stated that the process begins as Hodgkin's disease but may become sarcomatous. Ewing's views are well known, especially in connection with Hodgkin's disease in the thymus.

Warfield and Kristjanson cited an unusual case in which the condition is claimed to have undergone a transition from lymphosarcoma to lymphatic leukemia and then to Hodgkin's disease. In Mueller's case 1 the condition was originally typical lymphogranuloma and later became large round cell sarcoma, many cells being present closely "resembling the giant endothelioid cells so frequently seen in Hodg-

kin's disease." In his case 2 the condition was between round cell sarcoma and Hodgkin's disease and later became typical lymphogranuloma. Yamasaki, Karsner, Welch and Levine were cited by him as reporting parallel cases. He believed that lymphogranuloma and round cell sarcoma of the lymph nodes are different expressions of the same disease process; he referred to the work of Kopsch in support of his views. Kopsch produced "a polymorphocellular sarcoma" in frogs by feeding them the larvae of Rhabditis pellis; he believed that the malignant changes were due to a toxin elaborated by the larvae. The sarcomas in these experiments arose from granulation tissue and might be designated as malignant granulomas.

Piney, who believed in the essential reticulo-endothelial nature of Hodgkin's disease, stated that the differences between Hodgkin's disease, lymphosarcoma and endothelioma may be of degree rather than of kind.

Cohnheim found a case of leukemia without leukemic changes in the blood; he originally suggested the name "Pseudoleukämie," in 1865. Since that time the term has at times been applied to cases of Hodgkin's disease. Warthin described the condition as a generalized (or localized) aleukemic lymphocytoma; Ewing considered it a systemic aleukemic lymphomatosis; Sternberg emphasized certain features and separated it from true Hodgkin's disease; Cabot described it as "a hyperplasia of specially hemopoietic tissue closely akin to leukemia, in fact, distinguished therefrom solely by the absence of leukemic changes in the peripheral blood." Symmers readily separated the two diseases microscopically.

The general trend of feeling is that pseudoleukemia is a faulty term and should no longer be employed. This is to be especially emphasized here, as the relationships of Hodgkin's disease are obscure enough without further ambiguity.

Relation to Syphilis.—Although a number of references have been made to the relationship of syphilis and lymphogranuloma, cases in which the two conditions are present tend to be isolated and are really no more frequent than might naturally be expected with any other disease. There is a large preponderance of negative over positive serologic findings: Cunningham, 7 cases, all negative; Baldridge and Awe, 46 cases, 3 positive; Simmons and Benet, 16 cases, 3 positive; Wallhauser, 25 cases, 2 positive; Burnam, 173 cases, 1 positive. Of a total of 268 cases, therefore, 9, or 3 per cent, were positive, which is a fair average for any group.

MacCallum, after a minute search, using Levaditi's method, found no spirochetes. The spirochetes described by White and Proescher have never been accepted although several workers have attempted verification; the general opinion is that the so-called spirochetes are but con-

nective tissue fibers. Löwenbach cited an instance of Hodgkin's disease with syphilis. Treatment brought about recovery. Jordan, Schamschin and Staroff reported a case in which the gross findings at autopsy did not separate Hodgkin's disease from syphilis, microscopic examination being necessary to show that the supposed gummas were really lymphogranulomatous nodules. I have seen a similar case. Simmons investigated the cases of Gowers, Hutchinson, Renvers, Vaquez and Bibierre, Iwanow, Fabian, Kawatsare and Roth. In none of them was there satisfactory evidence of the implication of syphilis in the development of Hodgkin's disease.

Relation to Mycosis Fungoides.—A relation of mycosis fungoides to Hodgkin's disease was suggested many years ago. Lerrede said that the problem of the two diseases is the same, and Ziegler believed that the entire disease picture of mycosis fungoides is only that of a variety of species of Hodgkin's disease, and that they are either very closely related or identical. Paltauf, Louis Berger, Wechselmann, Hazen and Strobel (who included a review of the literature) and others were impressed by the possible identity or relationship of the two. Ketron, Gillot, Cornill and Renvier, and Pardee regarded mycosis fungoides as a lymphadenosis. Ceelen and Zurhelle described mycosis fungoides with visceral lesions. Arndt and Arzt separated the two, as did Berger and also Pardee and Zeit.

Vasiliu and Goia described an interesting case in which the clinical manifestations were those of mycosis fungoides and biopsy showed typical Hodgkin's disease. They followed Ranvier's belief, expressed in 1869, that mycosis fungoides is to be considered as a cutaneous form of Hodgkin's disease. However, they considered the term mycosis fungoides as too comprehensive, embracing several distinct conditions, as at one time the term pseudoleukemia did. Regarding this, Udo Wile (discussing a paper by H. E. Miller) stated that "mycosis fungoides is a useful clinical term and should be retained to differentiate tumors that tend to slough." Dühring, in 1888, referred to the condition as an "inflammatory fungoid neoplasm," which appears to apply to the clinical picture even today. He was impressed by the early inflammatory symptoms and later by the developments of a sarcomatous aspect.

Fraser considered mycosis fungoides to be a reticulum cell sarcoma of the skin and presented 2 cases in which the changes were unquestionably neoplastic. He brought evidence to show the genetic relationship between mycosis fungoides, lymphatic leukemia and lymphosarcoma. The suggestion to call lymphosarcoma a reticulum cell sarcoma is based on the assumption that the lesion in the skin has its origin in the reticulum cells of the papillary layer, the reticulo-endothelial system of the skin.

In connection with lymphosarcoma, Breakey cited a case of mycosis fungoides in which the two conditions were found together.

Keim classified mycosis fungoides with the true lymphadenotic infiltrations of the skin, including leukemia, lymphosarcoma, Hodgkin's disease, Sternberg's leukosarcoma and Kaposi's lymphoderma perniciosa. He held that the multiple clinical pictures associated with these diseases should be regarded as the variable expressions of the lymphoblastomas. In this connection McCarthy aptly remarked that "mycosis fungoides passes through so many different stages and shows so many phases of each state that it is not surprising that it may simulate very closely a large group of diseases at one time or another." This statement in my opinion also applies at times to true Hodgkin's disease.

No mention is made in the literature, to my knowledge, of mycosis fungoides in children. Borsutzky and Corbrille did not mention it, although cases of Hodgkin's disease in children are numerous.

Concerning the bacteriology of mycosis fungoides, Ausspitz reported a micrococcus; Vidal and Perrin, a staphylococcus; Rindfleisch, a micrococcus (in blood culture); Kubel, during life, a bacillus, and after death, a staphylococcus; Chevrel, a nonacid-fast, gram-negative coccobacillus; Verfasserin, from blood and tissues, both living and dead, an acid-fast rod that quickly became transformed into a nonacid-fast, gram-positive coccus. Busni reported the finding of a peculiar organism in 5 cases of mycosis fungoides and in 140 cases of lymphogranulomatosis. This bacterium in culture at first showed acid-fast forms, later appearing as a coccus, resembling Staphylococcus. This coccus did not return to the acid-fast form in vitro but had to be passed through an animal before it could be recovered in acid-fast form, and constitute constant findings. Busni regarded mycosis fungoides and lymphogranuloma as closely related, and both as bacteremias.

Differentiation between mycosis fungoides and lymphogranuloma is at times difficult (Fox; Ziegler; Miller). This may be true also on microscopic examination. McCarthy discussed this question in some detail. In typical cases of lymphogranuloma in which there is granulation tissue with numerous Sternberg giant cells the diagnosis can be made without difficulty. When these cells are absent, however, it may be almost impossible to separate the two conditions. In such cases the following considerations may be of value: In mycosis fungoides, in the eczematoid and beginning infiltration stages, in addition to the general findings, one may see many large lobulated, polymorphonuclear cells which are very similar to the Sternberg cell. However, in the tumor stage these cells are practically absent, which is in sharp contrast to the finding of large numbers of Sternberg cells in the tumor stage of lymphogranulomatosis. In mycosis fungoides the pleomorphism of the cell picture is most marked in the first stages, while in the tumor stage

the infiltrate has a more uniform make-up, being almost entirely composed of lymphocytic elements and connective tissue granulation cells. In the tumor stage the glands and internal organs show large numbers of eosinophils. Such a finding is absent in Hodgkin's disease. McCarthy further differentiated leukemic processes by the purely lymphocytic character of the infiltrate, by the absence of connective tissue proliferation and by the findings in the blood. Gans also differentiated lymphogranulomatosis and mycosis fungoides microscopically. In lymphogranulomatosis the nuclear and protoplasmic detritus is not found as in mycosis fungoides; moreover, the lesions undergo regression by caseation and necrosis, while in mycosis fungoides they disappear by absorption without caseation.

The question of a relationship between lymphogranulomatosis and mycosis fungoides must remain open. Certainly the clinical diagnosis of mycosis fungoides is frequently difficult or impossible, even for the most expert workers. I feel that Vasiliu and Goia have placed an interpretation on this relationship that harmonizes with the known facts very well—that mycosis fungoides is too comprehensive a term, embracing possibly several distinct conditions, but that a certain number of cases of what is commonly called mycosis fungoides must be considered as cutaneous forms of lymphogranulomatosis. In the latter statement they agree with Paltauf, Unna and Louis Berger. Until absolute criteria can be established for both diseases the question must remain open. Two recent cases reported by Milian illustrate this: The clinical diagnosis was mycosis fungoides, but on histologic examination of enlarged nodes, a diagnosis of lymphogranuloma was made. Markowitz made an interesting clinical comparison of the two diseases.

Relation to Myeloid Leukemia.—The possible relationship between lymphogranuloma and myeloid leukemia has been given some attention. Symmers stated that Hodgkin's disease and myeloid leukemia "are probably different quantitative responses to the same type of provocative agent," which is in accord with his theory that Hodgkin's disease has its origin in the bone marrow. In this connection Medlar's megakaryoblastic theory seems to require consideration, but at present no definite statement can be made. To those who hold to the infectious and also to the tuberculous nature of the disease, the work of Marshall and that of Twort may be stimulating. Marshall described a case of acute miliary tuberculosis showing the blood picture of myeloid leukemia. Twort inoculated 12 guinea-pigs with leukemic tissue and found that 6 had tuberculosis as a result.

Relation to Lymphatic Leukemia.—Cases have been described involving an apparent transformation of Hodgkin's disease into lymphatic leukemia (Wende; Warthin; Bunting and Yates). Burnam, who cited

173 cases of Hodgkin's disease, had never seen this occur, and he expressed the belief that the two diseases were quite different pathologic states. Richter's case of generalized reticular cell sarcoma of the lymph nodes was associated with lymphatic leukemia. He interpreted this as representing a leukemia of long standing, undiscovered, with the development of a rapidly growing malignant tumor superimposed. This explanation is stimulating when applied to the same problem in Hodgkin's disease. MacCarty's cytologic studies led him to believe in a close relationship between lymphatic leukemia, lymphosarcoma and Hodgkin's disease. Chute placed Hodgkin's disease, lymphosarcoma, lympho-epithelioma and leukemia under the name "malignant lymphoma," agreeing with the concept that these are but different forms of the same disease.

In conclusion, I again stress Ewing's view that strict adherence to histologic distinctions should be maintained, certainly in the absence of any known etiologic agent.

Relation to Tuberculosis.—The question of a relation of lymphogranuloma to tuberculosis is still highly unsettled, and discussion of it constitutes a considerable portion of the literature. The reports are so variable, and at times so entirely contradictory, that it is difficult to place them in an orderly and correlated sequence. I have therefore attempted to reduce the several phases of the question to statements of a categoric nature, referring to such articles as may bear on each division.

Rolleston presented the historical developments of the general knowledge of lymphogranuloma and briefly considered the possible etiologic relation to tuberculosis. Morgagni, in 1769, undoubtedly knew of the condition, but necessarily confused it with other lymphadenopathies. In Hodgkin's own series of 7 cases, Fox recently found unquestionable evidence of tuberculosis of the lymph nodes. Dickinson, in 1878, was the first to indicate that in cases of lymphogranuloma the tubercule bacillus may be considered as a secondary invader, but the modern controversy actually began with Sternberg's publication in 1898, in which he considered lymphogranuloma as a peculiar form of tuberculosis, in much the same way that lupus is a cutaneous form of tuberculosis, a view that has been actively supported and combated ever since. Sternberg has somewhat altered his contention at times, but he recently reaffirmed his original theory. Fraenkel and Much's finding of what they considered a granular form of the tubercle bacillus gave added strength to Sternberg's views, although many authors, notably Twort, have questioned both the presence and the significance of these granules. Animal inoculation has played a considerable part in the various attempts to decide the question, but the results are most confusing. Recently the problem has been brought to the fore by the negative find-

ings of Twort, the work of Vasiliu in support of Sternberg's theories, the immunologic studies of Stewart and Doan and the suggestion by L'Esperance that the disease may be caused by the avian tubercle bacillus.

In addition, a large amount of work has been done in investigation of the life cycle and of the possibility of a filtrable form or product of the tubercle bacillus, which to some observers is of importance in this connection. Other points will be considered later.

The various phases of the general relationships between lymphogranuloma and tuberculosis may be categorically stated in an affirmative sense as follows:

1. Lymphogranuloma is of tuberculous origin and represents a peculiar and atypical reaction of the host to the human type of B. tuberculosis or to a peculiar form of the same, as typified in the original view of Sternberg.

2. Lymphogranuloma and tuberculosis, either healed or active, are often found in the same patient (Ewing).

3. There is frequently a strong family history of tuberculosis.

4. Patients with lymphogranuloma often present tuberculous stigmas and lesions.

5. Acute tuberculosis often develops terminally in cases of lymphogranuloma.

6. Acid-fast rods, closely resembling B. tuberculosis, are found in lymphogranulomatous nodes (Sternberg).

7. Much's granules are found in lymphogranulomatous tissue and represent a form of B. tuberculosis (Fraenkel and Much).

8. Animals inoculated with lymphogranulomatous material will succumb to tuberculosis, which may be typical or atypical (Sternberg; Fraenkel and Much).

9. In acute tuberculosis, lesions are sometimes seen that are much like those of typical lymphogranuloma (Medlar and Sasano).

10. The hyperplastic form of lymph node tuberculosis may be almost indistinguishable from lymphogranuloma microscopically (Karsner; Rolleston).

11. Tuberculosis is a secondary invader in cases of lymphogranuloma, and is not etiologic (Dickinson; Longcope).

12. Tuberculosis finds in patients with lymphogranuloma a soil that is favorable for its development (Gilbert and Weil).

13. There is a facultative symbiosis between B. tuberculosis and the unknown etiologic agent of lymphogranuloma (Hirschfeld).

14. Avian tubercle bacilli are etiologic (L'Esperance).

15. The patient's capacity of reaction to the toxin of B. tuberculosis is the chief factor in the production of lymphogranuloma (Näslund).

16. Lymphocytes act on the tubercle bacillus, so altering its power of producing the classic picture of tuberculosis that instead it produces the peculiar histologic process of lymphogranuloma (Lichtenstein).

17. Lymphogranuloma may be produced by the "filterable elements of the tuberculous virus" (Martinolli).

18. Lymphogranuloma may be due to a degenerated form of B. tuberculosis, in which "this degenerate perhaps passes over into a diphtheroid type that is practically a distinct species." The disease is caused by this organism only in a particular type of host (Sweany [this view is no longer held by him]).

19. Lymphogranuloma causes an anergy whereby the patient's reaction to tuberculin is rendered negative, even when tuberculosis is present (Morquio).

20. The occurrence of lymphogranuloma and tuberculosis in the same patient, the tuberculosis being of the terminal generalized type, may be explained by the view that lymphogranuloma favors tuberculous infection or activates it when latent (Rolleston).

21. Lymphogranuloma is unlike tuberculosis in that it is not transmissible by methods used at present (Longcope; Stewart and Dobson; Cunningham and McAlpin; Twort; Tyzzer).

22. Occasionally in guinea-pigs inoculated with lymphogranulomatous material tuberculosis occurs showing lesions closely resembling those of lymphogranuloma. These lesions are atypical lesions of true tuberculosis (Schütt).

23. Lymphogranuloma is unlike tuberculosis in that family histories of lymphogranuloma are exceedingly rare.

24. The reaction to tuberculin in patients with lymphogranuloma is uncertain.

25. Tubercle bacilli, probably bovine, may be demonstrated in lymphogranulomatous material by repeated passage through guinea-pigs (Sticker).

26. Lymphogranuloma is a tumor process in which tuberculosis plays the part of an excitant (Stahr).

27. Lymphogranuloma is an expression of an atypical tuberculosis produced by toxins from inert or nonextending foci. The tuberculosis sometimes seen late in the disease may be a flare-up of this focus or a return to type of an atypical lesion (Paisseau, Valtis and Saenz).

The possible etiologic significance of the human tubercle bacillus in lymphogranuloma has been considered affirmatively by Sternberg, Crowder, Ferrari and Comotti, Steinhaus, Schur, Türk, Hitschman and

Stross, Fraenkel and Much, and more recently by Vasiliu and Goia. It may be stated that definite proof is lacking, not only in this but in many of the other divisions listed. Briefly, the evidence used in support is as follows: The histologic appearance of lymphogranuloma is not incompatible with an infection such as tuberculosis, and furthermore is that of a granuloma; giant cells similar to those in lymphogranuloma are seen in certain lesions of tuberculosis; acid-fast rods are present in some cases of lymphogranuloma; Much's granules are seen in some cases of lymphogranuloma; inoculation with lymphogranulomatous material frequently causes tuberculosis in animals; lymphogranulomatous patients often present tuberculous stigmas and lesions and have family histories of tuberculosis; the two diseases are often found together in the same patient, and generalized tuberculosis may often develop terminally; by repeated passage of lymphogranulomatous material through guinea-pigs, tubercle bacilli, probably of the bovine type, may at times be demonstrated; avian tubercle bacilli are claimed to have been demonstrated by inoculation of animals and fowls with lymphogranulomatous material.

All of these points have been questioned, and some of them absolutely contradicted. Clarke began the active discussion against this view, and many others have carried it on (Reed; Longcope; Simmons; Fischer; Butlin; Yamasaki; Schottelius; MacCallum; Duval and Howard; Twort; Terplan and Mittelbach; Fox and Farley; Baldridge and Awe; Frates and Galli; Sussig; Lange and others). The most exhaustive recent report is that by Twort, who attempted to duplicate the work of Fraenkel and Much, but who had decidedly negative results.

It is true that lymphogranuloma and tuberculosis are found together in the same patient, and Ewing's well known statement that "in New York where the disease is very common tuberculosis follows Hodgkin's disease like a shadow" must be given due weight. Sternberg and others found this combination commonly. Ziegler obtained family histories of tuberculosis in 10 per cent of cases, and found the diseases co-existent in 20 per cent. Lemon cited 191 cases of lymphogranuloma, with clinical tuberculosis in but 8 cases; Schreiner and Mattick, with 46 cases, and Burnam, with 173 cases, found the combination very infrequently. Baldridge and Awe noted it in but 2 of 46 cases, and found active fibrocaseous tuberculosis in none of 150 cases of "lymphoma." I have encountered clinical tuberculosis in but 2 of over 30 cases. To carry the investigation further, I examined 151 autopsy reports from the literature: Tuberculosis, active or healed, was present in 31 cases and absent or not demonstrated in 120. This gives an average of about 25 per cent, a little higher than Ziegler's 20 per cent.

Recently Parker, Jackson, Bethea and Otis analyzed an extensive series of cases in which autopsy was performed and offered statistics in

support of the close association of the two diseases. Healed and active tuberculosis is "significantly greater in Hodgkin's disease (33.3 per cent) than in other types of lymphoma (5.3 per cent) or in cancer (14.6 per cent) or general autopsies (19.3 per cent)." They emphasized their finding that "malignant lymphoma of other types (not Hodgkin's disease) is never associated with active tuberculosis."

A comparison of the incidence of tuberculosis among the public at large with tuberculosis as seen in patients with lymphogranuloma may be of value here. Baldwin, Petroff and Gardner drew conclusions from a number of extensive surveys and stated that in large numbers of people, 1 per cent have active tuberculosis and 1 per cent have recognizable but arrested tuberculosis, or that 2 per cent have demonstrable lesions. Rokitansky long ago demonstrated tuberculosis in a large percentage of routine autopsies. The results of the von Pirquet test as performed on the general public show about 90 per cent positive reactions. Another feature of interest is the demonstration by Gardner that tuberculous lesions may resolve, heal and disappear. In this laboratory at autopsy tuberculosis has been grossly demonstrable in 36 per cent of cases in general during a period of fifteen years.

These figures are compatible with those given in a preceding paragraph for lymphogranuloma. In 267 cases of lymphogranuloma, tuberculosis was demonstrable clinically 12 times—i. e., in 4.5 per cent—and tuberculosis, healed or active, was demonstrated post mortem in 25 per cent of 151 cases of lymphogranuloma in which autopsy was performed. Active terminal tuberculosis, however, especially in the generalized form, is a not unusual finding, and really should be considered separately. The results of tuberculin tests are not parallel, as negative reactions apparently preponderate in the presence of lymphogranuloma, which recalls the occasional negative reactions in the presence of unquestionable tuberculosis; the relationship remains obscure. Regarding the coincidence of tuberculosis and all forms of malignant growths, Fortune found in the examination of lengthy series of records that active tuberculosis is combined with malignant growths in about the same number of cases as with any other major fatal disease, and that healed tuberculosis is present in about the same number of cancerous as of noncancerous patients. Simonds found that sarcoma combined with tuberculosis in the same patient was reported rarely. I fully realize that fallacy occasionally results from reasoning on the basis of statistics, but the percentages cited for tuberculosis and for lymphogranuloma appear sufficiently close to indicate that tuberculosis occurs with lymphogranuloma in considerably fewer cases than has been commonly supposed, and that the coincidence approaches the normal expectancy. It is unfortunate that large numbers of completely detailed clinical and autopsy reports

of cases of lymphogranuloma are not available for analysis; only by such study can a true comparison be established, clarifying this debated matter.

The question naturally arises as to the possibility of overlooking tuberculous lesions in the presence of a preponderating and closely simulating mass of lymphogranulomatous tissue. Lubarsch showed that B. tuberculosis may be detected by animal inoculation in the absence of grossly demonstrable tuberculosis. Clinically this is, of course, easily possible, and even at autopsy it is understandable. Of interest in this connection are the reports of Schütt and Sweany, both of whom found minute, single, isolated tuberculous lesions, and also those of Kusunoki and Ewing, who found tuberculosis in single lymph nodes immediately adjacent to typical lymphogranulomatous nodes. The significance of these observations cannot be overestimated, for without such painstaking search the tuberculous lesions would undoubtedly have been missed and the patients described as free from tuberculosis, yet animals inoculated with material from them would conceivably have shown tuberculosis. Barron's statement is pertinent in this respect, that possibly glandular tuberculosis is more common in some locations than in others, which would serve to explain the markedly positive results of inoculation obtained by Sternberg, Fraenkel and Much, and others, in contrast to the negative results of Twort, Terplan and Mittelbach, and others. Not only may this remark be true, but many of the positive results may be analogous to those in the cases just mentioned in which undiscovered tuberculosis was present, and so accounted for the positive results of inoculation. Kaufmann has called attention to the possible accidental and unavoidable admixture of lymphogranulomatous and tuberculous tissue.

Another group of papers of similar significance includes those of Loomis, Opie and Aronson, Pizzini, and Kälble, Macfayden and MacConkey, who showed that "normal" lymph nodes frequently contain living tubercle bacilli capable of producing tuberculosis in animals. Bloomfield found numerous bacterial forms in normal lymph nodes, and Twort stated that although lymphogranulomatous nodes might contain tubercle bacilli, they perhaps as frequently contained streptococci or diphtheroids. Certainly with these facts in mind, animal inoculation experiments seem to lose much of their value in this problem.

Bovine tuberculosis has been suggested by Sticker, who used repeated passage through animals to demonstrate the organism. Lanken described canine tuberculosis in which enormous numbers of acid-fast rods were found in the mesenteric lymph nodes, the histologic picture of which resembles closely that of lymphogranuloma. These organisms could not be cultured, and they showed decreased pathogenicity on repeated passage through animals. I encountered a case of bovine

tuberculosis involving the hip joint in which well defined and generalized lymphogranuloma was a later development.

Avian tuberculosis has recently been advanced by L'Esperance as an etiologic possibility. Essentially the evidence in favor of this is: 1. Chickens inoculated with lymphogranulomatous material show typical avian tuberculosis, and inoculation of material from these chickens into other chickens causes a more marked and extensive tuberculosis with involvement of the bones. Cultures of material from the second group of chickens give a pure growth of culturally avian tubercle bacilli. 2. In guinea-pigs treated with killed human tubercle bacilli prior to inoculation with lymphogranulomatous material, an atypical tuberculosis of the lymph nodes develops and cultures on egg medium show many characters of avian tubercle bacilli. 3. Subcutaneous inoculation of rabbits with original lymphogranulomatous material causes no infection, as frequently happens with pure cultures of avian tubercle bacilli. The conclusion drawn from these experiments is that "this may indicate that the etiologic agent in certain forms of Hodgkin's disease is pathogenic for birds, or that the avian tubercle bacillus is a factor in producing some of the lesions which are interpreted as Hodgkin's disease." Utz and Keatinge attempted to confirm this work and were inclined to believe in the etiologic rôle of a bacillus closely resembling the avian type of tubercle bacillus. Branch, however, could not come to this conclusion. He included an extensive survey of avian tuberculosis. In an article on avian tuberculosis in rabbits, Medlar stated that the presence of myeloid giant cells, which are megalokaryocytes, in the spleen, liver and lungs, suggests a similarity between the process and Hodgkin's disease. Mayo and Hendricks described 2 cases of avian tuberculosis in man, in both of which the patients recovered following splenectomy. Other cases of avian infection in man have been noted occasionally. Baldwin, Petroff and Gardner stated that there has been a considerable increase of tuberculosis in chickens during recent years, which must be considered in experiments in which these birds are used. Petroff also hesitated to designate the avian tubercle bacillus as a true separate strain. Avian tuberculin has been used both as a test material and therapeutically.

In the course of my own work, 6 chickens inoculated with lymphogranulomatous material did not show tuberculosis after several months' observation. Nocard, and later Wiener, rendered human and bovine tubercle bacilli virulent for chickens by placing the cultures in colloidal sacs and enclosing these in the peritoneal cavities of hens. The sacs were removed after several weeks, cultured on potato and again placed in the peritoneal cavities of hens. After three passages they had become sufficiently virulent to infect a chicken seriously. Bang also observed the apparent transformation into avian tubercle bacilli.

Stewart and Doan used the phosphatid fraction of the lipoids of the tubercle bacillus as an antigen in testing serum from tuberculous patients, the test being a precipitin reaction. In 9 patients with lymphogranuloma on whom the tests were made, "the presence of free phosphatid-antigen was suggested in tests with antisera for avian phosphatid, four of the cases giving also a positive precipitin reaction with antihuman tuberculo-phosphatid serum. This observation would lend support to L'Esperance's finding of the avian tubercle bacillus in certain Hodgkin's cases." This work should be of interest to all students of the disease, especially as it presents a new avenue of attack.

The possibility that the disease may be due to an atypical, degenerate or other altered form of B. tuberculosis has been widely discussed since Sternberg's first report. Weigert, in 1884, demonstrated in lymphogranulomatous nodes organisms that resembled the tubercle bacillus; Fraenkel and Much believed that Much's granules were really the granular form of B. tuberculosis. Kahn observed in vitro the development cycle of a single tubercle bacillus and described forms that resemble diphtheroid bacilli morphologically, coccoid types and granular, nonacid-fast forms that closely resemble the granules of Fraenkel and Much. Sweany had already recognized mutation forms, much the same as those seen by Kahn; he suggested that the diphtheroid bacilli of Billings as well as the granular forms of Fraenkel and Much may be degenerated tubercle bacilli. He described the isolation of two types of acid-fast bacilli from the same case: a "smooth" moist type resembling the avian variety, but avirulent for all common animals (including chickens) except guinea-pigs, in which large doses produced death with a tuberculosis-like pathologic picture, and a second type which was unstable at first but which became like the human type. Twort attempted to heighten the virulence of certain acid-fast bacilli, especially Mycobacterium phlei, with negative results. The virulence was not affected by injection of lymphogranulomatous, cancerous or leukemic tissues. He further found that lymphogranulomatous material in fluid culture mediums had no noticeable effect on the surface growth of B. tuberculosis and allied saprophytes. The peculiar organism described by Busni, while not believed to be the tubercle bacillus, somewhat closely resembles it. The possibility of a filtrable form was considered by Vasiliu and Goia and by Martinolli. It is questionable whether there is a true filtrable form, according to several writers. Gloyne, Glover and Griffith stated that Fontès, in working with Much's granules, first suggested the possibility; they concluded, however, that a filtrable form does not exist.

Probably a majority of students of the disease (notably, Reed, Longcope, Lemon and others) have considered B. tuberculosis as a secondary invader. This view is tenable, although it is not proved,

especially when the great incidence of tuberculosis is realized, more particularly the healed and quiescent types containing viable tubercle bacilli. If it is true, as many believe, that the lymphoid and reticulo-endothelial systems are concerned in the defense against tuberculosis, it is hardly surprising that a lighting up of a tuberculous focus should occur when these systems have been practically eliminated or seriously injured by a disease such as lymphogranuloma. The duration of viability of the bacilli after growth has ceased, as in healed lesions, is not known, but in artificial cultures it generally is less than two years. In the body it must be much longer, if only to account for the facts as seen in lymphogranuloma. The most usual active tuberculous lesion found in lymphogranuloma is the acute miliary or submiliary type occurring late or terminally, which is compatible with this theory.

The histologic relationships were considered under the heading of histology, to which the reader may refer. Reference may also be made to the section on tuberculin tests.

Space will not permit a more extensive discussion of this highly important aspect, for the material already at hand could easily be made to yield a sizable monograph. One of my chief objects in offering this somewhat extended presentation was to call attention to the numerous and complex ramifications of what at first appears to be a direct question of etiologic relationship. It is evident that it is much more.

Tuberculin Tests.—Tuberculin tests have given uncertain results. Positive results were obtained by Biuclin, Baumler-Diehl, Halstead, and Simmons; negative results by Beitzke, Weill and Lesieur, Simmons, Lehndorf, Osler, Reed, Ruffin, and Sauler. In 2 cases in which pleurisy was present, Morquio reported 2 negative results. Borsutzky found the von Pirquet test negative in two thirds of cases in children; Corbeille corroborated this, saying that in none of his cases were there definitely positive results. MacNalty gave the patient in his case 0.00005 mg., which he increased to 0.0001 mg., every ten days with no effect. Rulison reported the use of three types of tuberculin; with the avian and the human type the reaction was positive, and with the bovine type it was negative; he suggested a possible skin test. It is interesting to note that a node from this patient was injected into a chicken, with no apparent effects in nine months of observation.

In a case which I recently observed old human tuberculin was used intracutaneously. The injection (0.01 mg.) was followed shortly by a profound constitutional reaction—rise in temperature, etc. Furthermore, on several subsequent occasions the same reaction occurred following similar injections. The histologic picture of a previously excised node was that of Hodgkin's disease and in no place did it suggest tuberculosis, the diagnosis being agreed on by three pathologists. From a clinical point of view, this could be interpreted only as a specific

reaction. The enlarged nodes decreased a little in size, but at no time presented the appearance of tuberculosis. I have noted but one other definitely positive reaction to tuberculin in a series of more than 30 cases. This occurred in a child who had tuberculous arthritis of long standing plus Hodgkin's disease. A positive, though not a marked, reaction was obtained with bovine tuberculin (intracutaneous injection). Tyzzer reported a negative reaction to tuberculin in a monkey which had been inoculated with an emulsion of tissue from Hodgkin's disease. White and Fox reported tests on 12 normal monkeys, with 37 per cent positive results. Morquio, in discussing the commonly negative results of the tuberculin test in Hodgkin's disease, stated "that lymphogranulomatosis causes a condition of anergy of the patient, by which the reaction to tuberculin is rendered negative, even when tuberculosis is present."

MEDICOLEGAL ASPECTS

Four cases present certain features of possible medicolegal interest involving trauma. One of these was reported by Hirsch: A man fell and fractured five ribs, which caused two months' disability. Six months later his condition was diagnosed as lymphogranuloma. Hirsch stated that the accident excited or stimulated a possibly preexisting lymphogranuloma of the hilar lymph nodes. The patient in Hendrick's first case injured both arms and the lower ribs. After some time enlarged nodes were seen, and biopsy showed Hodgkin's disease. The patient in Hendrick's second case fell, experiencing pain in the inguinal region, abdomen and chest. On examination, an inguinal hernia was found, and operation was performed. A short time later the patient complained of pain in the splenic region. An irregular fever, anemia and enlargement of the lymph nodes and spleen developed, with dulness over the base of the left lung. Death occurred three months after operation. Autopsy showed Hodgkin's disease. Hendricks claimed, however, that the trauma had no causal relationship, although both of his patients drew workmen's compensation. His second case presented other unusual and interesting features of a medicolegal nature. One of my cases had its onset just after an accident. A young woman injured her thigh. This was followed by enlargement of the inguinal lymph nodes and then by the development of a rather large pelvic mass. Two well qualified pathologists considered that the biopsy showed Hodgkin's disease, but I have always believed that the condition was sarcoma. Death was preceded by generalized enlargement of the lymph nodes.

CLINICAL AND GENERAL PATHOLOGIC ASPECTS

Although in this review adequate consideration cannot be given to the purely clinical phases of the disease, a number of interesting and

unusual observations encountered in the literature may be mentioned. The field of pathology has already been covered by numerous authors and has received attention under various subheadings in this review. A few reports of particular interest are included here.

MacNalty's detailed work on the peculiar pyrexia is of importance; Rolleston supplemented this and included a special bibliography. In Abrahams' case the condition closely resembled typhoid, a finding occasionally mentioned by others (Ziegler; Muller and Boles; Weiss; Isaacs). Creevy took up the question of irregular fever in general, and found that this type was not confined to lymphogranuloma but occurred especially in hypernephroma. Barron's case 1 showed a curious cyclic fever with intervals of three weeks, which suggested an infection with an animal parasite. He mentioned the rarity of this type of fever and cited MacNalty, Whillington, and Longcope as having seen similar cases. Abrahams cited a case with periodic pyrexia. Subnormal temperature was noted in a case by Simmons and Benet. Cunningham found normal temperatures in 13 cases during the period of observation. Fabian found the Pel-Ebstein type of fever in 50 per cent of cases. Desjardins and Ford observed fever in 31.3 per cent of a series of 135 cases. Barron found fever in about 50 per cent of 24 cases. Jackson contributed information on the occurrence of fever.

Odd manifestations have occasionally been encountered: subcutaneous emphysema (Baldridge and Awe); tachycardia of persistent rate (Dumas, Bernay and Boucaumont); paroxysmal abdominal pain (Fox and Farley; Whillington); backache as an early symptom (Isaacs); albuminuria without lymphogranulomatous lesions in the kidneys (Vasiliu and Goia); perforation of an intestinal ulcer (McAlpin and Von Glahn); mild neuralgias as a common symptom (Burnam); paroxysmal tachycardia as the first symptom, due to fatty degeneration of the vagus resulting from pressure by a mediastinal mass (Graber; MacNalty; Murchison; Ebstein; Pel); epistaxis (Barron); vocal disturbances (Chatellier); involvement of the breasts (Marimón; Kückens; Kaufmann); corneal infiltration (Lagrange; Morax); orbital involvement (Reeves; Simmons and Benet); perforation of the wall of the chest (Lyon); generalized miliary form (Gsell).

Clinical classifications in general follow Trousseau's earliest (1865) division into latent, progressive and cachectic stages. Ziegler's work is well known. Other studies are those of Cunningham, Vasiliu and Goia, and Favre. Symmers contributed a detailed paper on the clinical significance of pathologic changes, offering a division of the disease into two types, the ordinary and the invading.

Acute cases are not the rule but do occur (Karsner; Clarke; Kretz; Hirschfield and Isaac; Howell [reported a case closely simulating acute appendicitis]; Whillington; Cunningham). Clinical variation without

corresponding qualitative histologic changes was seen in acute and chronic cases by Baldridge and Awe. In their opinion, acuity tended to have an inverse relationship to the age of the patient.

Jaundice occasionally occurs as a symptom (Pepper; Longcope; Gsell; Coronini; Barron [who found peribiliary infiltration at autopsy]).

Conditions simulated by lymphogranuloma and thus confusing the diagnosis are numerous. This phase has been discussed by Whitaker, Baldridge and Awe, and Holler and Paschkis, who reported an unusual case simulating hemolytic jaundice.

Recession in the size of the enlarged nodes was commented on by R. C. Cabot, who found it in the nodes and in the spleen when an acute infection occurred during the course. I have seen it occasionally following diagnostic biopsy. Messick and Furrer reported the absence of any enlargement of the superficial or mediastinal lymph nodes in the presence of a retroperitoneal involvement.

TREATMENT

Surgical Treatment.—There are advocates for and against the surgical removal of lymphogranulomatous tissue. Yates, and Yates and Bunting spoke in favor of radical operative treatment, especially in cases showing single rather than multiple distribution. Larrabee cited a case in which splenectomy was performed with good results, there being but small nodes in the neck. Tandberg described resection of the upper lobe of a lung, followed by roentgen irradiation. Minot and Isaacs, in evaluating the results of surgical treatment alone or plus irradiation and of irradiation alone in cases of lymphoblastoma, stated that in patients treated by surgical intervention, whether irradiation was used or not, the average duration of life following treatment was 3.67 years, 1.11 years longer than the average of 2.56 years without this treatment. They suggested that surgical procedures are most likely to be used when the disease seems to be localized, has progressed slowly or is not extensive. "It is just such cases that seem by nature to be destined to last relatively long." Burnam stated that surgical intervention alone has no value aside from furnishing biopsy material, and that extirpation not followed by roentgen irradiation usually means rapid recurrence. Sussig was in full accord with him in this, but put emphasis on radical surgical intervention and on medical treatment as well as on irradiation. Borsutzky, and Fischer expressed themselves as against surgical treatment, considering it useless and productive of acute recurrences. I had a patient who showed marked enlargement of the right side of the neck within a few days after a radical extirpation on the left side of the neck. Cases are recorded, however, in which this did not occur. Muller and Boles believed that radical operation is to be considered when external evidence indicates that the disease is chronic and nonprogressive, when

some function is interfered with by pressure, and when splenomegaly persists after irradiation. Weil advocated laminectomy in certain cases of spinal involvement.

Drugs.—Since Murchison, in the belief that the condition was a form of tuberculosis, treated a patient with quinine, iron and cod liver oil, numerous remedies have been tried. Some have apparently helped, and others have had no effect. Iodine, iron, phosphorus, colloidal metals, benzene, sodium salicylate, methenamine, emetine hydrochloride and emetine bismuth iodide have all been unsuccessful. The arsenicals have long been used—arsenic trioxide, colloidal arsenic trisulphide, sodium acetyl arsanilate, arsphenamine, neoarsphenamine, sodium cacodylate and sodium arsanilate. At times improvement or remission has been seen with the use of neoarsphenamine, and occasionally with some of the other arsenicals. No cures are claimed, however. Chevallier reported some palliative effects from the use of antimony, apparently better than those obtained with arsenic. Grasso could not obtain any effect with antimony. Acetylsalicylic acid is of value in controlling pruritus. Cod liver oil is used in the same manner as in tuberculosis. I used chaulmoogra esters in a case, but without success.

Biologic Preparations.—Erysipelas and prodigiosus toxins (Coley) have been tried with little effect or with results of doubtful value.

Ovarian extract was offered by Gemmell as a means of increasing resistance in females; he also used an extract of the lymphatic glands internally. This will be discussed further under gynecology.

Radioactive Substances.—Stevens claimed good results with intravenous injections of radium chloride. The use of thorium X subcutaneously and of thoron intravenously may be mentioned also. These substances must be considered as dangerous in view of the well known effects of radium poisoning, even when very small amounts are absorbed (Martland).

Ten Doornkaat-Koolman advocated repeated sojourns at high altitudes plus roentgen therapy; he obtained a remission of four years' duration in a case in which this treatment was used. Ernst attempted to adjust the patient's vitamin balance, in addition to giving roentgen therapy. It seemed that small doses of x-rays produced much more marked results when such a balance was effected. He used a diet rich in vitamin B, plus enemas containing Bacillus tumefaciens, chosen because of its high content of vitamin A. No claims were made as to cure.

Transfusions of blood have often been used for the anemia. Burnam, reporting 173 cases, stated that they should rarely be resorted to. Sharp reactions are frequent even when the blood is most carefully matched; death occurred in 1 case. My own experience is in agreement; I believe blood transfusions to have only transitory value.

Vaccine and Serum Therapy.—Numerous attempts have been made to use the diphtheroids isolated from the lymph nodes as vaccines. Billings and Rosenow, Hatcher and Lemon, Fox, Cunningham, Mellon, and Bunting and Yates reported variable results. After a fairly comprehensive review of the literature, the feeling is perhaps justified that bacterial vaccines of this type at times possibly produce remissions. Their action is too uncertain, however. One cannot lose sight of the important fact that remissions frequently occur without any treatment. This statement must always be considered in attempting to evaluate any therapy in Hodgkin's disease. Cunningham stated the general feeling toward vaccines of C. hodgkini: "They have had a fair trial, but since this organism is not the specific cause it seems futile and a waste of time and material to continue."

Lortat-Jacob and Schmite proposed the injection of the serum from an irradiated patient with Hodgkin's disease into another patient not yet irradiated, roentgen therapy being given after the injection. The erythrocyte count was definitely improved.

Schreiner and Mattick used autolyzed lymph nodes as a vaccine, with no results. Wallhauser and Whitehead used sterile lymph node filtrates, with variable effects; however, they apparently obtained remissions in some cases. Hanrahan, who used the same method, felt that possibly remissions were obtained at times. In a series of cases I noted effects which were favorable in some instances and distinctly unfavorable in others. No cures can be claimed. Grapiolo and Tenconi obtained favorable remissions through the injection of extracts of macerated glands.

Miller's report on 2 cases of Hodgkin's disease is most interesting; one of the patients was well for ten years following an attack of erysipelas; the other was moribund but recovered after an attack of severe gangrenous herpes zoster. The observations leading to the advocacy of erysipelas and prodigiosus toxins (Coley) are somewhat parallel. Certainly some profound reactions may at times initiate remissions which can hardly be coincidental in all cases and which appear at times to resemble those seen in sarcomatosis.

HODGKIN'S DISEASE IN LOWER ANIMALS

Few cases are recorded, possibly because of insufficient search. In investigating the Slye stock of mice, Simonds found 316 cases of enlargement of the lymph nodes and spleen in 15,000 autopsies. He found 4 mice which showed a condition closely resembling the disease as seen in man, although he refrained from making a positive diagnosis. The histologic picture generally was that of replacement of the lymphocytes by large cells. The spleen was enlarged; in 3 animals the liver showed periportal infiltration by lymphocytes and large cells, and in 1

there was a mass of the same cells in the hilus of the kidney. Krebs, Rask-Nielsen and Wagner recently undertook a study of lymphosarcomatosis in white mice which is of interest in attempting to correlate lymphosarcoma, leukosarcoma, lymphatic leukemia and lymphadenosis. They described a lymphatic leukemia in the mice which is transferable from generation to generation in strongly irradiated animals, and which may appear sometimes as lymphosarcoma, as leukosarcoma or as lymphadenosis. They suggested the name "lymphomatosis infiltrans (leukemica or aleukemica)" and believed that there is a close relationship between the disease in mice and that seen in man. The recent attention to avian tuberculosis gives interest to Ellermann's work on the leukemias of fowls. He stated that the chicken has no lymph nodes, and that the mass of apparent lymphoid tissue in the neck is really thymic tissue. Lanken described a case of canine tuberculosis with a nonculturable virus, in which the histologic picture of the lymph node closely resembled that of Hodgkin's disease. Many acid-fast rods were found, but they could not be cultivated, although a series of guinea-pigs into which they were injected were affected.

Other references to the disease in lower animals are given in the bibliography of Simonds.

DEATH

The manner and the time of death depend on several variable factors, chiefly the course (acute or chronic), the organs and situations involved, the degree of anemia, secondary infections, the quality of the patient's resistance and the treatment. The subject is therefore too extensive to be taken up completely here. A remarkable case of sudden death was described by MacCallum in discussing Paullin's paper. The patient had areas of softening in the ribs. "One day the patient was sitting up in bed and he leaned forward to drink a cup of tea, when he suddenly died." The autopsy showed that the odontoid process of the axis was completely severed by erosion, and the slight effort had dislocated the vertebral column so as practically to cut the cord in two. Cases of sudden death are numerous, but in none of those reported was death as instantaneous as in MacCallum's case. Some common causes of death are: suffocation as the result of a large mediastinal tumor pressing on the bronchi and trachea (Weber); generalized peritonitis from perforation of an intestinal ulcer in lymphogranulomatosis of the gastro-intestinal tract and acute anemia from hemorrhage (Hayden and Apfelbach); acute pulmonary edema; bronchopneumonia, and an acutely speeded up cachexia. Ginsburg correctly stated that in acute cases death usually occurs not by "a proliferative compressive phenomenon, but by a severe toxemia which presented all the characteristics

of an acute infectious disease." Heissan, Levy, Hendricks, Whillington and Howell cited acute cases that are of interest in this connection.

In chronic cases, the picture is somewhat different. The immediate cause of death varies with the case. Generally anasarca, delirium of varying degree, pleural effusion and icterus are symptoms that may immediately precede death (MacNalty). Cunningham stated that the final state may present a picture of acute toxemia with high intermittent fever, the temperature becoming subnormal for several days before death. I saw a case in which the patient remained fully conscious up to within two hours of death and 2 cases in which excessive irradiation unquestionably hastened the end. In one of these the patient was so severely burned that the anterior abdominal wall was partially necrotic. Another patient who had been in coma suddenly had a remission two days prior to death. He became fully conscious, strong and alert enough to sit up and shave himself; he then passed slowly into a progressive coma. No 2 cases are quite alike, and death unquestionably ensues from a variety of factors.

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Notes and News

University News, Promotions, Resignations, Appointments, Deaths, etc.—In the medical school of the University of Georgia a department of bacteriology has been established with James A. Kennedy at the head.

F. Blumenthal, director of the Institute for Cancer Research in Berlin, has accepted the appointment as professor in the faculty of medicine in Belgrade, where he will continue his experimental work in cancer.

Hans Zinsser, professor of bacteriology and immunology in Harvard Medical School, has been given the degree of doctor of science by Lehigh University.

George H. Hansmann, assistant professor of pathology in the University of Iowa, has been appointed associate professor of pathology in Georgetown University, Washington, D. C.

Frederick G. Novy has assumed the deanship of the medical school of the University of Michigan.

Twenty fellows are now working under the Medical Fellowship Board of the National Research Council.

Bernhard Zondek, whose name is associated with the hormone test for pregnancy, is now consulting gynecologist to the Victoria Memorial Jewish Hospital in Manchester, England.

Albert Calmette, assistant director of the Pasteur Institute in Paris and originator of the B C G vaccine against tuberculosis in infants, has died at the age of 70.

Friedrich Fülleborn, director of the Institut für Schiffs- und Tropenkrankheiten in Hamburg, well known investigator in tropical medicine, especially helminthology, died on Sept. 9, 1933.

Society News.—The Second International Conference on Geographic Pathology will be held in Utrecht, Holland, in July, 1934. The subject for discussion will be arteriosclerosis.

The American Association for the Advancement of Science will meet in Boston from Dec. 27, 1933, to Jan. 2, 1934.

The Society of American Bacteriologists will hold its thirty-fifth annual meeting in Philadelphia, Dec. 27 to 29, 1933, under the presidency of William Mansfield Clark.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE EFFECTS OF RADIUM IRRADIATION ON TISSUE CULTURES. W. G. WHITMAN, Am. J. Cancer **17**:932, 1933.

Tissue cultures were exposed to radium emanation in varying doses. Since most of the beta rays were eliminated by filters, the effects were due almost entirely to the gamma rays. The normal fibroblasts showed the characteristic fall and recovery in mitotic count after irradiation, depending on the dosage and the length of exposure. Cells in division at the onset of irradiation proceeded in a normal fashion to complete mitosis. Abnormal mitotic figures, consisting of pyknotic, shrunken and clumped chromosomes, were found shortly after irradiation. Scattered, aberrant and lagging chromosomes, with the formation of nuclear fragments and chromosomal vesicles, were also characteristic of irradiated cultures. It is suggested that possbily some of these changes during karyokinesis may be due to an injury or a change in the consistency of the spindle substance. No damage was observed to mitochondria or nucleoli following irradiation. Cultures of Walker rat sarcoma 338 were exposed to 5, 16 and 50 millicurie hours. Similar morphologic changes were noted, but such changes occur also in nonirradiated cultures. In addition, the irradiated tumor cultures appeared unable to live if the medium was changed after irradiation. The normal cells (macrophages) appeared to be more affected by these doses than did the tumor cells. The number of mitoses of the normal cells (macrophages) was proportionately more reduced by irradiation than that of the malignant cells. The percentage initial fall in the mitotic count for the normal cells was greater for all three doses than for the malignant cells.

AUTHOR'S SUMMARY.

A CLASSIFICATION OF THE DISEASES OF LIPOID METABOLISM AND GAUCHER'S DISEASE. LUDWIG PICK, Am. J. M. Sc. **185**:453, 1933.

The xanthomatoses are divided into two groups, namely, generalized and localized. The generalized forms consist of (1) the symptomatic or secondary forms, those which accompany other diseases and are manifestations of disturbances of lipoid metabolism associated with these diseases, and (2) the essential or primary forms, those which constitute disease entities in themselves and are based on a constitutional anomaly of lipoid metabolism. In this group belong (*a*) Gaucher's disease, (*b*) Niemann-Pick's disease (*c*) Hand-Schüller-Christian's disease and (*d*) the primary nonsymptomatic external and internal xanthomatoses which occur in varying distributions and intensity in the skin and in the internal viscera. The morphologic picture of Gaucher's disease consists of the deposit of the typical, large, fat-containing Gaucher's cells in the spleen, liver, lymph nodes and bone marrow, resulting in enlargement of the spleen and liver and in nodular or diffuse collections of cells in the marrow cavities, especially of the long bones. The Gaucher substance is optically and microchemically inactive. Mandelbaum's dictum, that a microchemical finding of neutral fat, myelin-like or doubly refractile substance in suspected cells excludes the presence of Gaucher's disease, still holds true. The Gaucher substance is essentially kerasin but contains phosphatides soluble in alcohol. The Gaucher cells arise from the reticulum cells of the spleen, lymph nodes and bone marrow as well as from the adventitial and periadventitial cells of the splenic arterioles. Pathogenetically, Gaucher's disease exemplifies a primary congenital and familial metabolic disturbance on a constitutional basis. The constitutional basis is indicated by the early onset, the familial occurrence, the predominance of the female sex and the susceptibility of the Jewish race.

SANDER COHEN.

PATHOGENESIS OF ERYTHROLEUCOSIS. H. L. RATCLIFFE and J. FURTH, with the assistance of C. BREEDIS, Am. J. Path. **9**:165, 1933.

Under the influence of a filtrable agent, the basophil erythroblasts of the sinusoidal capillaries of the marrow undergo unrestricted multiplication. The erythroblasts thus formed fail to mature. They crowd out all other elements of the marrow, secondarily invade the circulation and accumulate in the capillaries of the internal organs, where they continue to multiply. Fowls inoculated with material containing erythroleukotic cells showed growth of the cells in the blood stream and the organs at a time when erythroblasts had only partly filled the capillary bed of the marrow. In fowls in which injections of the cell-free material had been made the blood did not contain these immature cells until the marrow was almost completely filled by them. With erythroleukosis, thrombocytes in the blood stream are at first increased and later much diminished or absent. With the disturbance of erythrogenesis, the formation of thrombocytes is inhibited.

AUTHORS' SUMMARY.

THE RELATION BETWEEN THE MITOCHONDRIA AND GLUCOSE-GLYCOGEN EQUILIBRIUM IN THE LIVER. E. M. HALL and E. M. MACKAY, Am. J. Path. **9**:205, 1933.

Disturbances of the dextrose-glycogen equilibrium in the livers of rabbits have been produced by feeding large quantities of dried and fresh carrots followed by periods of fasting, by dextrose feeding to fasting animals and by injections of epinephrine into fasting animals. Excessive amounts of glycogen, as high as 13.1 per cent, were obtained in the animals fed dried carrots. Amounts ranging from 3.5 to 5.7 per cent were obtained in the animals fed fresh carrots and in those given dextrose. Injections of epinephrine produced mainly glycogenolysis. Marked changes in the mitochondria were found in the animals fed dried carrots. Instead of the usual short bacilliform rods, long filaments, coarse spherules and plump rods were found condensed about the nucleus and, to a lesser degree, about the cell membrane. Twelve hours of fasting in this group produced coarse spherules without a definite arrangement in the cytoplasm. Many of the spherules appeared to be semifluid. Administration of dextrose caused hypertrophy and enspherulation of mitochondria, with some tendency to paranuclear arrangement. We conclude that some relation exists between the mitochondria of the hepatic cell and the dextrose-glycogen equilibrium. Whether or not the chondriosomes act as catalysts, as they appear to do in the synthesis of fat within the hepatic cell, we are unable to say.

AUTHORS' SUMMARY.

PIGMENT DEPOSITS IN INTESTINAL MUSCLE IN RELATION TO DIET. E. NACHTNEBEL, Am. J. Path. **9**:261, 1933.

A peculiar brown or buff pigmentation of the muscle coats of the intestinal tract has been observed in dogs. Some of the dogs had bile or Eck fistulas with or without anemia. Other dogs were in the anemia colony of the laboratory and had been continuously anemic from bleeding for various periods. Other dogs were normal. Age was not a factor. Microchemical reactions and staining properties of the pigment are given. On the basis of these tests one observes some similarity to the pigment observed in human disease (hemofuscin) and in old age. It is suggested that the pigment is not a definite entity but perhaps a pigment complex. The experiments indicate that it is of dietary origin due to some hepatic constituent which is absorbed. Observations on cases of anemia in human beings when large amounts of liver or liver fractions have been administered should prove of interest.

AUTHOR'S SUMMARY.

PASSAGE OF LIQUIDS FROM THE STOMACH TO THE INTESTINE. J. STEWART and W. N. BOLDYREFF, Am. J. Physiol. **102**:276, 1932.

From observations made principally on dogs with gastric fistulas, the following results are reported: Gastritis and duodenitis produce marked inhibition of gastric evacuation; even plain water was retained for from two to three times the normal period and was not exceeded in rapidity of evacuation by other fluids. No essential differences were observed in the evacuation of acids and alkalis of corresponding strengths. The emptying was prolonged by alcohol, mustard, pepper and other spices, certain bitter salts and peptone. The temperature, within a range from 2 to 50 C., had little effect on the emptying time. Duodenal regurgitation was found to be the most important factor in the neutralization of gastric acidity.

H. E. EGGERS.

EMPTYING OF THE GALL BLADDER. A. S. MARRAZZI, Am. J. Physiol. **102**:293, 1932.

In normal, fat-fed cats on which operation had not been performed the extent of the emptying of the gallbladder was studied by quantitative estimation of the bile evacuated. Additional studies were made of unanesthetized trained dogs by a new method of abdominal endoscopy, the endoscope being inserted through a trocar opening. The observation failed to show muscular contraction of the viscus while it was being emptied, nor was emptying produced by the administration of drugs stimulant to the smooth contraction of the muscles, nor by mechanical or electrical stimulation.

H. E. EGGERS.

MECHANISM OF ACTION OF PARATHYROID HORMONE. D. I. THOMSON and L. I. PUGSLEY, Am. J. Physiol. **102**:350, 1932.

It was found that the increase of serum calcium in dogs after the injection of parathyroid hormone is not necessarily associated with a decrease of total inorganic phosphate in the serum. When that is increased by the administration of dextrose and insulin, it causes only a slight increase of the calcium. The rate of disappearance from the blood stream of injected calcium does not appear to be affected by the simultaneous injection of the hormone, nor is the subsequent action of the hormone in the raising serum calcium apparently modified by the injection of the calcium. Apparently the hormone does not act by increasing the solvent action of the plasma for the calcium compounds of bone; the authors suggest that its effect may be stimulation of the osteoclastic process of bone.

H. E. EGGERS.

A PHYSIOLOGICALLY ACTIVE SUBSTANCE APPEARING DURING ANAPHYLACTIC SHOCK. C. A. DRAGSTEDT and E. GEBAUER-FUELNEGG, Am. J. Physiol. **102**:512 and 520, 1932.

In these two articles the authors report that in the majority of cases of severe or fatal anaphylactic shock in dogs there appears, in the supradiaphragmatic vena cava and in the thoracic duct, a substance or substances which have the property of stimulating smooth muscle; the substance disappears rapidly, as the blood circulates, and only rarely can it be detected in the blood from the femoral vein. A series of tests of the substance, reported in the second paper, led to its identification in all probability as histamine.

H. E. EGGERS.

THE EFFECTS OF OVERDOSAGE OF IRRADIATED ERGOSTEROL. J. H. JONES and G. M. ROBSON, Am. J. Physiol. **103**:338, 1933.

Rats of from 68 to 138 days of age were fed an excess of viosterol sufficient to cause death in periods of from six to eight weeks. Examination of the femora showed marked degenerative changes, with greatly increased porosity due to the

removal of both the organic and the inorganic matrix, apparently by increased osteoclastic activity. There was a relative decrease of ash, which was apparently the result of the subsequent growth of osteoid tissue after the absorption of the bony matrix. The administration of large but nontoxic doses of viosterol to young rats on a diet low in calcium did not produce to any degree changes in the absolute amount of ash. Relatively the amount of ash was increased over that of rats that had been given the same basal diet without supplement, but the cause of the difference was greater development of osteoid tissue in the latter animals. The vitamin D under these circumstances would appear to restrain the overgrowth of osteoid tissue, failure to calcify being here due to insufficient calcium in the diet. In the animals receiving the vitamin D, the amount of blood calcium remained about normal, but in those which were given the basal diet alone it fell below 7 mg. per hundred cubic centimeters.

H. E. EGGERS.

PEPTIC ULCERS (GASTRIC, PYLORIC AND DUODENAL) IN GUINEA-PIGS. DAVID T. SMITH and M. MCCONKEY, Arch. Int. Med. **51**:413, 1933.

Routine necropsies on 1,000 guinea-pigs maintained on our stock diet failed to show a single spontaneous peptic ulcer. Of 75 guinea-pigs fed diets deficient in vitamin C, in 20, or approximately 26 per cent, peptic ulcers developed which were similar in location and in gross and microscopic appearances to those observed in man. Of 80 guinea-pigs fed corresponding basic diets supplemented by vitamin C, in only 1 did peptic ulcer develop. Diets deficient in vitamins A, B and D did not cause peptic ulcers if the supply of vitamin C was adequate. Mechanical injury to the mucosa of the duodenum in guinea-pigs fed an adequate diet was followed by rapid and complete healing, while similar injury to guinea-pigs fed a diet deficient in vitamin C resulted in the formation of peptic ulcers. Peptic ulcer in the guinea-pig is apparently caused by a partial but prolonged deficiency of vitamin C.

AUTHORS' SUMMARY.

EXPERIMENTAL PYLOROSPASM AND GASTRIC RETENTION IN RATS. F. HOELZEL and E. DA COSTA, J. Exper. Med. **57**:597, 1933.

A method was found whereby the development of gastric retention could be studied in intact animals without the necessity of recourse to the use of x-rays. Gastric retention was found to develop as a result of the restriction of protein in seven of ten rats studied. Such retention could again be cleared up by protein realimentation or by allowing the animals free choice of protein, fat and carbohydrate. A diet high in protein following periods of undernutrition or prolonged restriction of protein usually gave rise to transient gastric retention. Diets with a solution of 25 per cent or more of alcohol added promptly gave rise to gastric retention in rats even when the protein content of the diet was adequate. Evidence is given indicating that the gastric retention which occurred in this study involved more or less pylorospasm, and possible influence of mechanical and chemical irritation and of the changes in the gastric mucin and in the flow of the bile on the development of pylorospasm are discussed. Spira's theory that fat in the diet gives rise to pylorospasm and ulceration is not supported by the results of the experiments.

AUTHORS' SUMMARY.

FACTORS IN THE HUMAN LIVER PRODUCING HEMOGLOBIN. G. H. WHIPPLE and F. S. ROBSCHEIT-ROBBINS, J. Exper. Med. **57**:637, 653 and 671, 1933.

The factors in the human liver which produce hemoglobin were estimated by feeding human liver to standardized anemic dogs under various conditions. It was found that acute infections reduce somewhat the hemoglobin-producing factors in the human liver; in arteriosclerosis, passive congestion, amyloid and fatty degeneration, carcinoma and cirrhosis with severe injury to the cells of the liver the

factors may be reduced. In untreated patients with pernicious anemia the factors producing hemoglobin may be increased in the liver; this is also true of aplastic anemia and secondary anemia due to destruction of the blood within the body.

THE LYMPHATIC PARTICIPATION IN HUMAN CUTANEOUS PHENOMENA. S. S. HUDACK and P. D. MCMASTER, J. Exper. Med. **57**:751, 1933.

A technic is described for the demonstration of lymphatic capillaries in living skin and for their study. By means of vital dyes injected intradermally the vessels can be rendered plainly visible. They form an extraordinarily abundant anastomotic web. The least scratch, one which does not penetrate through the epidermis, gives rise to such conditions that lymphatic absorption readily takes place from the abraded surface; and so close-meshed is the lymphatic web that an intradermal injection with even the finest hypodermic needle tears some of the constituent vessels open, with the result that they undergo direct injection. In many persons much of the fluid introduced at an ordinary intradermal injection, like that made in the clinic, spreads through the superficial lymphatic network, whereas in others it tends to enter the deeper lymphatics at once, the difference being due to merely physical factors determined by the texture of the skin. Normal flow along the lymphatics of the skin is rapid even when the body is at rest, dye introduced into the skin of the resting forearm reaching the axilla within a few minutes. The observations make plain the fact that every intradermal injection is an intralymphatic one, often preponderantly such, while, furthermore, every local injection into the skin becomes within a few minutes a general one, so rapidly is the introduced material transported to the blood. The normal permeability of the lymphatics of the skin of man is approximately the same as that of the mouse. Tests indicate that in both instances the lymphatic wall behaves like a semipermeable membrane. The permeability of the human lymphatic wall, like that of the mouse, is subject to rapid and great changes. A stroke on the skin with a blunt instrument to produce a wheal causes the lymphatic capillaries to become so permeable temporarily that dyes pass through their walls as if practically no barrier existed, instead of being held back for a greater or lesser period. Slight inflammation due to heat, ultraviolet rays or bacterial products has a similar effect. So, too, has histamine. When fluid pours rapidly into the tissue from the blood, as when a wheal is formed, the lymphatics are compressed, and their efficiency as drainage channels is interfered with. These facts are briefly discussed as to their bearing on cutaneous phenomena in general. The lymphatics cannot be disregarded in considering such phenomena, in which it is plain that they have a large share.

AUTHORS' SUMMARY.

MODERN TESTS OF LIVER EFFICIENCY APPLIED TO EXPERIMENTAL SHALE OIL LIVER NECROSIS. CYRIL POLSON, Brit. J. Exper. Path. **14**:24, 1933.

The following modern tests of the efficiency of the liver were applied to rabbits that had acute necrosis of the liver due to the administration of shale oil: the phenoltetrachlorphthalein test, the rose bengal test, the van den Bergh reaction and the levulose and galactose tolerance tests; the urea and amino-acid concentration of the blood was also determined. The development of an opalescence of the serum during the experiment precluded examination of the rose bengal test and limited observation of the phenoltetrachlorphthalein test. The results obtained with the latter prior to experiment showed that it was unlikely to be a reliable test. Coincident renal dysfunction was responsible in some measure for the increase in the urea concentration of the blood, and prevented an estimation of the severity of the dysfunction of the liver. A high concentration of amino-acid in the blood indicated gross damage to the liver, but it was observed only as a terminal phenomenon. The results of the levulose tolerance test were equivocal, and it was not until the fourth day that unqualified positive results were obtained. A positive result was invariably associated with gross damage to the liver, but severe damage

was present in a rabbit that gave a negative reaction on the third day. The galactose tolerance test was negative in two rabbits that had necrosis of the liver, but the lesion was invariably present when the test was positive. Damage to the liver was clearly indicated by this test, even on the second day of experiment in three of the five rabbits. Of the seven tests examined, this one is most likely to give a reliable indication of the presence of damage to the liver, and is probably able to detect damage of less severity than that which produced positive results in the other tests.

AUTHOR'S SUMMARY.

THE FAILURE OF PROLONGED ADMINISTRATION OF IRON TO CAUSE HAEMOCHROMATOSIS. CYRIL POLSON, Brit. J. Exper. Path. **14**:73, 1933.

The iron content of the livers of thirty-six adult rabbits was maintained at a high level for from one to four years. The terminal level in ten rabbits under experiment for from three to four years ranged from 3.42 to 7.67, and averaged 5.19 per cent dry weight. Cirrhosis of the liver and pancreatic damage were absent from all. It is therefore shown that excess of iron in the body over long periods caused neither cirrhosis of the liver nor hemochromatosis in rabbits, and it is unlikely that excess of iron is responsible for the hepatic and pancreatic lesions of human hemochromatosis.

AUTHOR'S SUMMARY.

MARROW ACTIVITY. A. E. BOYCOTT and C. L. OAKLEY, J. Path. & Bact. **36**:205, 1933.

Transfusion reduces the number of reticulocytes in the circulating blood; living in atmospheres with an excess of oxygen does the same. There is an intimate inverse relationship between the concentration of hemoglobin and the proportion of reticulocytes in the blood. Neither the persistent polycythemia resulting from repeated transfusions nor living in air rich in oxygen leads to the complete disappearance of reticulocytes from the blood. Rats do not become substantially anemic after living in air containing 65 per cent of oxygen.

AUTHORS' SUMMARY.

INFLUENCE OF SEXUAL HORMONES ON THE NUMBER OF BLOOD PLATELETS. GEORG BANKOW, Beitr. z. path. Anat. u. z. allg. Path. **88**:113, 1932.

The thrombocyte count in normal white rats varies between 180,000 and 220,000 per cubic millimeter. It is decreased during fasting and is highest four hours after feeding. The number of the thrombocytes is lower during the summer than during the winter. In both sexes, removal of the sexual glands or ligation of their blood vessels causes a marked decrease of the blood platelets which last two months. By subcutaneous injection of extracts of the sexual glands, the number of thrombocytes is markedly increased and reaches its maximum thirty-five days after injection. After this period the number decreases slowly and is again normal at the end of the second month.

C. ALEXANDER HELLWIG.

PHYSIOLOGY AND PATHOLOGY OF THE PALATINE TONSIL. HERMANN HOEPKE, Beitr. z. path. Anat. u. z. allg. Path. **88**:207, 1932.

In the normal tonsil, the centers of the lymph follicles are germinal centers, producing small lymphocytes from reticulum cells and lymphoblasts. In the chronically inflamed tonsil, the germinal centers are transformed into reactive centers. The formation of small lymphocytes decreases or ceases entirely. As a defense reaction against bacteria and toxins, only reticulum cells and macrophages are produced, and the reactive centers attain considerable size when the irritation is of long duration. The capsule is thickened and impedes the emigration of newly formed cells, which appear threadlike. The cells are carried by stagnating

lymph fluid to the periphery. There is a stagnation in the lymph and in the blood vessels, and there may be even a retrograde lymph flow, causing rupture of the lining epithelium of the tonsil.

C. ALEXANDER HELLWIG.

INFLUENCE OF FREEZING ON THE TESTIS OF THE GUINEA-PIG. T. J. ARJEW, Beitr. z. path. Anat. u. z. allg. Path. **88**:395, 1932.

Ethyl chloride sprayed on the testes of guinea-pigs produces degenerative and productive changes in the sex cells and in the interstitial tissue. In the periphery, the entire epithelial wall of the seminiferous tubules is destroyed. In the central portions of the gland, the spermia die first, then the spermatids, spermatocytes and the spermatogonia, in the order named. The Sertoli cells are highly resistant and may remain intact in the otherwise necrotic tubules. The interstitial tissue reacts against freezing temperature in the first stage by producing an exudate and by proliferation of cells. Hemorrhages are found in the tunica albuginea and in the interstitial tissue. During the reparative stage, many multinuclear giant cells are formed by the spermia and spermatids. The Sertoli elements do not undergo mitotic or amitotic cell division. The interstitial tissue finally replaces the necrotic seminiferous tubules by scar tissue.

C. ALEXANDER HELLWIG.

EFFECT OF ROENTGEN RAYS ON THE SPLEEN OF THE FROG AND SALAMANDER. P. W. SSIPOWSKY, Beitr. z. path. Anat. u. z. allg. Path. **88**:413, 1932.

The intensity of the lesions in the spleen following irradiation corresponds to the dosage of the x-rays. It is also dependent on the intensity of the rays. Irradiation produces necrobiosis of the lymphocytes and hypertrophy of the reticulum cells; there are pyknosis, karyorrhexis and finally complete fragmentation of the erythrocytes. The number of pigmented cells and hemocytoblasts is increased. Owing to the destruction of erythrocytes, the reticulum cells of the spleen and liver contain a great amount of iron.

C. ALEXANDER HELLWIG.

EFFECT OF THYROXINE ON YOUNG WHITE MICE. HANNA SCHULZE, Beitr. z. path. Anat. u. z. allg. Path. **90**:142, 1932.

White mice received daily subcutaneous injections of thyroxine from the day of birth to the time of sexual maturity. The dosage was increased progressively and varied in different animals. Mice appear to be highly resistant to the acute toxic action of thyroxine. Litters were reduced to four, two of which were kept as controls. The control animals received daily injections of sterile physiologic solution of sodium chloride. The animals treated with thyroxine were stunted, as compared with their litter-mate controls, but their development was more rapid, as determined by the time of appearance and the rate of growth of the incisor teeth. Marked changes were noted in the hair and skin of the thyroxinized animals. Their hair became wooly, and much of it was lost. The bald patches of the skin became ulcerated. The eyelids became inflamed and finally closed. Both male and female animals treated with thyroxine were sterile. Precocious union of the epiphysis and diaphysis of the bones led to dwarfing of the skeleton. The thyroid and thymus were smaller than those of control litter-mates. The heart was hypertrophied. The other internal organs revealed only inconstant changes. Microscopic examination of the testes and ovaries is not recorded.

O. T. SCHULTZ.

EXPERIMENTAL CHANGES IN LYMPHOID FOLLICLES. E. JECKELN, Beitr. z. path. Anat. u. z. allg. Path. **90**:244, 1932.

The animals used in Jeckeln's experiments were chiefly guinea-pigs. The experimental procedures consisted in the subcutaneous or intraperitoneal injection of diphtheria toxin, the subcutaneous injection of killed cocci (pneumococcus or

staphylococcus vaccine) and the oral administration of sodium fluoride. The author is convinced that the state of the lymphoid tissues may vary in animals of the same species and age kept under identical conditions. To overcome this factor, in one series of experiments small pieces of the spleen were removed before the injection of diphtheria toxin and other pieces at various times after injection. The results of the experiments have a bearing on the controversy over whether the centers of the lymphoid follicles are true germinal centers in the sense of Flemming or are secondary reaction centers in the sense of many recent writers. The earliest change noted by Jeckeln, following mild stimuli, was a state of lymphatic hyperplasia, characterized by transformation of the center of the follicle into a germinal center, in which there occurred a production of lymphocytes from lymphoblasts. More severe or more prolonged action led to nuclear fragmentation, which was most marked in the center. This phenomenon was followed by transformation of the follicle into a reaction follicle, characterized by proliferation of the reticulo-endothelial cells of the follicle.

O. T. SCHULTZ.

EXPERIMENTAL MALFORMATIONS OF THE CHICK EMBRYO. V. PAPILIAN and A. NANA, Virchows Arch. f. path. Anat. **287**:5, 1932.

The authors gave a brief description and histologic study of maldevelopments of the brain and the heart of four chick embryos after centrifugation of the eggs for periods of from three to five minutes. The resulting maldevelopments are explained as due in part to inhibition of development and in part to tumor-like proliferation of the tissue.

O. T. SCHULTZ.

DIETARY PROTECTION AGAINST NECROSIS OF THE LIVER DUE TO ARSPHENAMINE. A. SCHRIFRIN, Virchows Arch. f. path. Anat. **287**:175, 1932.

One group of dogs was maintained on a diet high in carbohydrate, another on a diet high in fat and a third on a diet high in protein (meat). The animals received intravenously from 0.03 to 0.04 Gm. of arsphenamine in alkaline solution per kilogram of body weight. Contrary to many statements in the literature, the diet high in carbohydrate did not protect the animals against focal necroses of the liver, as it was less efficacious in this respect than the diet high in protein. The diet high in fat rendered the animals susceptible to hepatic damage; it was found that the van den Bergh reaction was not a satisfactory index of the degree of damage. The damage is primarily entirely parenchymatous; the stroma reaction is secondary.

O. T. SCHULTZ.

PATHOLOGIC STATES ENCOUNTERED AMONG CHINESE. J. HEINE, Virchows Arch. f. path. Anat. **287**:203, 1932.

This article is a report of the kinds of pathologic lesions encountered in the examination of 1,064 specimens from the surgical operating room and from 106 necropsies. All the subjects were Chinese. The work was done in the pathologic institute of Hung Chi University in Shanghai. The author expresses the belief that variations in the frequency and the character of different diseases among the Chinese, as compared with western races, bear no relation to hereditary constitutional racial factors, but are probably due entirely to external factors.

O. T. SCHULTZ.

ERYTHROPOIESIS IN ENDEMIC GOITER. S. I. SCHERMANN, Virchows Arch. f. path. Anat. **287**:363, 1932.

In 160 patients with endemic goiter in the Mari Territory of central Russia, reticulocyte counts were made by Schilling's method. The author believes that this is the best method of determining the erythropoietic function of the bone

marrow. In ninety-one patients a moderate increase in the reticulocytes was found. The finding of an increased erythropoietic activity of the bone marrow in hypofunction of the thyroid is contradictory to the common opinion that hypothyroidism exerts an inhibiting effect on the function of the bone marrow. It seems likely that the thyroid excretion does not exert any direct action on blood-forming organs.

W. SAPHIR.

Pathologic Anatomy

EXTENSIVE DECALCIFICATION OF THE BONES IN AN EIGHT YEAR OLD BOY. A. J. ABELOFF, I. P. SOBEL and A. BERNHARD, Am. J. Dis. Child. **45**:105, 1933.

A case of unusual and extensive rarefaction of the bones is reported in an 8 year old boy. Specimens were removed from the distal femoral metaphyses. Sections of decalcified bone showed widening of the marrow spaces with rarefaction of the trabeculae. The marrow was for the most part of the ordinary fatty type, though in localized areas it was fairly rich in cells. A few of the marrow spaces were occupied by loose vascular granulation tissue, and the corresponding trabeculae were bordered by osteoclasts. However, there was not sufficient evidence to warrant a diagnosis of fibrous osteitis, the ratio of the calcium excreted in the urine to that eliminated in the feces being normal. The blood calcium was not elevated. Study of the calcium and phosphorus metabolism revealed subnormal retention.

RALPH FULLER.

INJURIES PRODUCED BY CONTACT WITH ELECTRIC CIRCUITS. ORTHELLO R. LANGWORTHY and WILLIAM B. KOUWENHOVER, Am. J. Hyg. **16**:625, 1932.

Rats were used in the study of injuries caused by contact with electric currents. Paralysis of the posterior parts of the body and of the extremities occurred frequently following shocks with high voltage alternating current. Postmortem examinations of paralyzed rats usually revealed the rupture of a small artery in the posteromedial septum of the cord, less frequently in the ventrolateral columns. The spinal cord possessed a characteristic appearance; in the upper thoracic and cervical regions the posterior columns appeared lavender, cross-sections revealing a large hemorrhage. Hemorrhage in the subarachnoid space was observed in a number of animals. On microscopic examination small hemorrhages were found in the substance of the brain, most commonly in the brain stem. Rather commonly there was rupture of the arteries of the choroid plexus with hemorrhage in the cerebral ventricles. Damage to nerve cells was more apparent after injury with continuous current. Sections of brain stained with thionine and hematoxylin and eosin showed various degrees of injury. In the cells most severely injured the nuclei were shrunken and stained an intense blue, so that the skeins of chromatin and the nucleoli could not be distinguished. In cells less severely injured the nucleoli were swollen and the nuclei shrunken and stained darkly. The injury seemed selective in that abnormal cells could be found among groups of comparatively normal cells and in that the Purkinje cells seemed most markedly injured.

RALPH FULLER.

A MICROSCOPIC STUDY OF THE TISSUES OF THE ALBINO RAT FOLLOWING THE INGESTION OF ALUMINUM SALTS. ERNEST SCOTT and MARY K. HELZ, Am. J. Hyg. **16**:865, 1932.

The conclusions reached in this study are based on the findings in eighty test and twenty-two control white rats which had received varying amounts of aluminum salts up to 3.6 per cent of their food by weight. The protracted ingestion of aluminum salts in concentrations as high as 3.6 per cent had no deleterious effect on the growth, reproduction or blood. The livers examined contained a normal

amount of iron. There was no gross or microscopic evidence in the organs examined of a pathologic condition which could be attributed to the ingestion of aluminum salts. Autolytic changes in the stomach and intestine occurred only when these organs contained partly digested food. Animals which had fasted for twenty-four hours before they were killed seldom showed this condition. We therefore found no lesions in the gastro-intestinal tract which could be attributed to the presence of aluminum.

AUTHORS' SUMMARY.

NOURISHMENT OF THE MYOCARDIUM THROUGH THEBESIAN VESSELS. S. BELLET, B. A. GOULEY and T. M. MCMILLAN, Arch. Int. Med. **51**:112, 1933.

The heart of a 16 year old boy is described in which an unusual degree of tuberculous fibrocaseous infiltration had destroyed the coronary arteries and the large surface veins. A system of sinusoids (thebesian vessels), many of which were dilated and some of which had thickened walls, connected the endocardium with the remaining intramural veins and furnished the only means of myocardial nourishment. The unusual pathologic cause of the obliteration of the coronary circulation (both arteries and veins) prevents a direct and exact comparison of the circulatory features of the heart described with those seen in double coronary occlusion of the more chronic types.

AUTHORS' SUMMARY.

NECROSIS OF THE SPINAL CORD PRODUCED BY ELECTRICAL INJURIES. O. R. LANGWORTHY, Bull. Johns Hopkins Hosp. **51**:210, 1932.

Anesthetized rats were subjected to alternating electric circuits at different potentials (from 18 to 1,000 volts), the contacts being made with the dorsal surface of the head and of the tail. Complete paralysis of the posterior portion of the body with incontinence developed in many of the animals. It is thought that the injury was caused by the direct action of the current on the spinal cord. The lesion, in general, remained confined to the posterior columns, although sometimes the whole cord became necrotic. The cavity contained relatively few red blood cells but many fat droplets and some amorphous débris. Similar cavities develop in the spinal cord of man as the effect of concussion after injuries suffered in war. The posterior columns appear to be particularly susceptible to injury, while the gray matter of the cord offers considerable resistance to the spread of the lesion.

AUTHOR'S SUMMARY.

ACUTE PNEUMOCOCCAL NEPHRITIS. S. S. BLACKMAN and G. RAKE, Bull. Johns Hopkins Hosp. **51**:217, 1932.

Acute nephritis was found in 9.4 per cent of ninety-five cases of pneumococcic infections (lobar pneumonia, organizing pneumonia, empyema, pericarditis, otitis media and meningitis). The microscopic character of the nephritis corresponds to that produced in rabbits by the intravenous injection of pneumococcus toxin. The kidneys of young children seem especially susceptible to injury by pneumococcus toxin. Outspoken examples of acute nephritis were found only in infants with pneumococcic infections, usually of long duration, other than pneumonia alone. The condition was not present in adults who had similar chronic pneumococcic infections. Slight or moderate changes, besides cloudy swelling, have been found in 76.8 per cent of the kidneys examined. This damage of slight degree, occurring in the kidneys of adults and children, differs only in extent from that found diffusely in the kidneys of infants with distinct acute nephritis.

AUTHORS' SUMMARY.

THE EXTRACARDIAC ANASTOMOSES OF THE CORONARY ARTERIES. C. L. HUDSON, A. R. MORITZ and J. T. WEARN, J. Exper. Med. **56**:919, 1932.

Widespread anastomoses of the auricular branches and the coronary branches to the pericardial fat with the pericardiacophrenic branches of the internal mammary

arteries and the anterior mediastinal, pericardial, bronchial, superior and inferior phrenic, intercostal and esophageal branches of the aorta have been described. The most extensive anastomoses between the cardiac and the extracardiac vessels are around the ostia of the pulmonary veins. It was possible not only to demonstrate the passage of an injected mass from the coronary arteries into the vessels of surrounding structures, but to show that the material passed into vessels in the heart from the thoracic branches of the aorta. This rich potential extracardiac coronary collateral circulation is probably of significance in compensating for sclerosis of the large trunks of the coronary arteries. [Four hearts with pericardial adhesions into which injections were made by way of the coronary arteries are described by A. R. Moritz, C. L. Hudson and E. S. Orgain (*J. Exper. Med.* **56**:927, 1932).]

AUTHORS' SUMMARY.

HEPATIC LESIONS IN ECLAMPSIA AND FROM RAISING INTRA-ABDOMINAL PRESSURE. G. W. THEOBALD, J. Path. & Bact. **35**:843, 1932.

Severe degenerative and necrotic changes in the livers of dogs, sometimes associated with hemorrhagic necroses in the periphery of the lobules, may be caused by frequently raising the intra-abdominal pressure to between 80 and 100 cm. of saline solution for thirty seconds or longer. It is probable that the hepatic lesions associated with eclampsia and the coincident hemorrhages in the other organs of the body are more often the result than the cause of the convulsions which may be initiated by the onset of labor. It is possible to account for the degenerative changes in the liver associated with hyperemesis gravidarum in a similar manner. The damage to the liver caused during the second stage of obstructed labor, and possibly in many cases of normal labor, is probably an important factor in lowering the resistance of the body to puerperal infection.

AUTHOR'S SUMMARY.

A CASE ILLUSTRATING THE EFFECTS OF PROLONGED ACTION OF RADIUM. J. M. ROSS, J. Path. & Bact. **35**:899, 1932.

A case is described in which a radium needle with a wall thickness of 0.5 mm. of platinum, containing 2 mg. of radium in the form of radium sulphate, had been embedded in the interventricular septum of the heart for three years. The pericardial cavity was almost obliterated by firm adhesions. A zone of necrotic heart muscle extended around the needle for a radius of 1½ inches (3.7 cm.). The changes in the heart muscle were apparently due to alterations in its blood vessels. The spleen and the lymphadenoid tissue showed: proliferation and activity of macrophages, loss of the follicular structure of the lymphoid tissue, disappearance of lymphocytes, and replacement of lymphocytes by plasma cells. It is suggested that these changes are a result of vascular disturbances induced directly or indirectly by irradiation. The blood picture after one year's irradiation showed relative and absolute lymphopenia. It is suggested that this is due to deficient production and to metamorphosis of lymphocytes into plasma cells. The liver was found to contain a malignant hemangio-endothelioma in a zone immediately subjacent to the needle. Metastatic growth was present in the lungs and bone marrow. The origin of the tumor can be traced to the endothelial lining of the branches of the portal vein. It is suggested that the growth was caused indirectly by the action of prolonged irradiation on the vessels near the surface of the liver. Finally, therefore, the case affords additional evidence that the necrotizing and carcinigenic action of gamma radiation results from the susceptibility of the vascular system to irradiation.

AUTHOR'S SUMMARY.

SCLEROPIGMENTARY FORMATIONS IN THE SPLEEN. D. S. ELEFTHERIOU, Ann. d'anat. path. **9**:1, 1932.

In a 40 year old woman who died of chronic nephritis and uremia, the spleen was atrophic, weighing only 70 Gm., but showed many areas of incrustation by

brownish-red iron pigment, with sclerosis and calcification, characteristic of so-called mycotic splenomegaly. Microscopic examination revealed a perivascular location of these areas, as well as a proliferating vascular stroma in the vicinity. The author believes the condition to be primarily vascular, resulting in successive hemorrhages. Whether the sclerosis represents a primary vascular injury or secondary organization could not be determined. The peculiar mycelium-like, fibrillar, reticular and spheroidal structures are considered to be degenerative, not mycotic. The chief points of view expressed in the literature on the subject are reviewed.

PERRY J. MELNICK.

A CASE OF "CATARRHAL" JAUNDICE WITH BIOPSY. A. SCHRUMPF, Ann. d'anat. path. **9**:17, 1932.

A 39 year old woman with catarrhal jaundice was operated on, on the eighth day of her illness, because of an incorrect diagnosis of cholelithiasis. A specimen of the liver was taken for biopsy. Microscopic study revealed a characteristic severe diffuse hepatitis, and not cholangeitis. This supports the newer view held by Klemperer, Killian and Heyd, and Eppinger.

PERRY J. MELNICK.

PROLIFERATING THROMBOPOIETIC ENDOVASCULITIS. FOLKE HENSCHEN, Ann. d'anat. path. **9**:113, 1932.

Henschen disagrees with the conception that so-called intravascular endothelioma is a tumor. From a study of many such lesions in hemorrhoids, urethral polyps and other conditions, he concludes that the endothelial proliferation results from a toxic or inflammatory stimulus. There is an associated thrombosis, but the latter can be followed through various stages and is seen to be secondary. Hence he proposes the name proliferating thrombopoietic endovasculitis.

PERRY J. MELNICK.

MYCOTIC SPLENOMEGALY. N. HORTOLOMEI, N. BALAN and T. BURGHELE, Ann. d'anat. path. **9**:145, 1932.

This critical review covers the subject thoroughly, and there is an extensive bibliography. From the heterogeneous group of conditions which went under the name of Banti's syndrome, namely, splenomegaly, anemia, hemorrhages, ascites and cirrhosis, Gamna of Italy, in 1922, separated an entity in which the spleen presents tobacco-colored nodules of iron pigment. (A case of this type had first been described by Gandy in 1905; hence the name Gandy-Gamna nodules.) Soon this condition was recognized in many other countries. It was differentiated in Algeria from kala-azar and in Egypt from bilharziasis. At first various organisms were thought to be etiologically concerned, but when peculiar mycelium-like structures were discovered in the lesions, a mycotic origin of the disease was accepted. Cultures and inoculation of animals have, however, given negative results. The portals of entry of the fungi are considered to be ulcerations of the skin or lesions of the gastro-intestinal tract which are frequently found associated. However, the fungi have also been considered to be secondary invaders associated with other primary conditions, such as Hodgkin's disease and leukemia. Furthermore, the mycotic origin of this condition has been strongly contested, the mycelium-like structures being considered artefacts. The authors present a case of their own.

PERRY J. MELNICK.

THE BONE MARROW IN CIRRHOSIS OF THE LIVER. JEAN ROSSIER, Ann. d'anat. path. **9**:245, 1932.

The author studied the bone marrow in thirty-nine cases of Laënnec's cirrhosis and in nine cases of cirrhosis of other types. In the majority (90 per cent) there was a peculiar hyperplasia of the bone marrow, namely, a dissociated reaction.

There was marked myeloblastic and erythroblastic proliferation, but a diminution of megakaryocytes and thrombocytopoiesis. The close resemblance of the picture to that of the bone marrow in pernicious anemia brings up the possibility of a primary or secondary toxic influence, perhaps associated with the liver. Other conditions may have an influence, such as repeated hemorrhages, hemorrhagic diathesis, various infectious conditions, for instance, chronic gastritis and biliary and hepatic infections, and also endocrine dysfunction. The last mentioned condition was especially studied by Barrelet with the same material; he found testicular atrophy and a decrease in the weight of the thyroid gland.

PERRY J. MELNICK.

CALCIFIED ECHINOCOCCUS CYSTS. PEDRO JAUREGUI and JOSÉ L. MONSERRAT, Ann. d'anat. path. **9**:345, 1932.

Four cases of calcified echinococcus cysts were studied in detail with reference to the perihydatid membrane, the process of calcification and histologic demonstration of calcium. The various theories of calcification are discussed as applied to the calcification of these cysts. The various methods for histologic demonstration of calcium are given, as well as a new method devised by Monserrat. Three photomicrographs show the crystalline structure of the calcium as demonstrated by Monserrat's method.

PERRY J. MELNICK.

THE GLANDS OF INTERNAL SECRETION IN CIRRHOSIS OF THE LIVER. J. BARRELET, Ann. d'anat. path. **9**:391, 1932.

The same material that was used by Rossier (*Ann. d'anat. path.* **9**:245, 1932) was studied by Barrelet with reference to the glands of internal secretion. The most important finding was atrophy of the testicles with proliferation of the interstitial cells in most cases. In women there was atrophy of the ovaries. The thyroid gland was markedly atrophic and was decreased in weight, with a decrease in the amount and a change in the character of the colloid. The hypophysis at times showed an increase in basophilic cells; the suprarenals, a decrease in lipoid, and the pancreas, an increase in connective tissue and occasional fibrosis of the islands.

PERRY J. MELNICK.

A CASE OF PSEUDOMYXOMA OF THE HEART. J. MONTPELLIER and R. RAYMOND, Ann. d'anat. path. **9**:511, 1932.

In a case of far-advanced pulmonary tuberculosis there was found attached to the endocardium of the left auricle a nut-sized mass which had the histologic structure of pseudomyxomatous tissue. The mass was interpreted to be not a tumor but a mural thrombus which was undergoing an abortive organization.

PERRY J. MELNICK.

ORIGIN OF THE SENILE PLAQUES OF THE CEREBRAL CORTEX. L. MARCHAND, Ann. d'anat. path. **9**:569, 1932.

Marchand made histologic studies in ten cases of senile cortical plaques, using the Bielschowsky, Hortega, Cajal and Weigert-Pal and other methods. The plaques never reach more than 80 microns in diameter and are almost confined to the gray matter. They consist of localized degenerative changes depending on vascular changes, especially arteriolosclerosis. The degenerative changes consist of an alteration in the fibrillar network of the gray matter, which becomes argyrophil; they result in the formation of lipoid droplets. Fibrillar and protoplasmic glia encroach on the plaque. The central portion is composed of an amorphous material resulting from the products of degeneration of various sorts of fibrils. In the pyramidal layer rodlike and granular particles are formed from the débris of the axis cylinders or neurofibrils. In the molecular layer giant astrocytes are found. There is no inflammatory reaction in the periphery of the plaques.

PERRY J. MELNICK.

PIGMENTARY CIRRHOSIS AND BRONZE DIABETES. MARCEL LABBÉ and MIRCEA PETRESCO, Ann. d'anat. path. **9**:697, 1932.

The authors present seven cases of pigmentary cirrhosis of the liver, of which five were classic cases of bronze diabetes. The constant factor in all was the cirrhosis and hemosiderosis of the liver. The pancreas also presented variable degrees of cirrhosis and hemosiderosis. The islands of Langerhans were absent in six cases. The spleen was generally only slightly or not at all affected. The lymph nodes were not involved except for those in relation to the liver and pancreas, which were converted into veritable "iron mines." The endocrine glands showed minor changes. The other organs were not affected. The various aspects of the disease are discussed.

PERRY J. MELNICK.

EXTRAGLANDULAR LESIONS OF LYMPHOGRANULOMATOSIS. PAUL FOULON, Ann. d'anat. path. **9**:725, 1932.

The author discusses the lesions of Hodgkin's disease of the liver, lung, spleen, bones and gastro-intestinal tract. In general, two modes of spread of the lesion are evident. The first is a circumscribed nodular form secondary to a lymphangitic metastatic process. The second is characterized by a diffuse activation of the potential reticulo-endothelial elements of an organ.

PERRY J. MELNICK.

ALTERATIONS OF BLOOD VESSELS IN TUBERCULOUS CAVITIES. M. KASPER, Beitr. z. Klin. d. Tuberk. **80**:537, 1932.

The protruding ridges in cavities frequently do not contain any vessels. The wall of the cavity is usually composed of three layers: first, a necrotic inner layer; second, a layer of granulation tissue, and third, a layer of connective tissue. The vascular alterations are different in the various layers. Within the cirrhotic tissue the adventitia is thickened. There is usually a cellular infiltration, most marked in the adventitial layer and least marked in the intima. In the granulation tissue the adventitia is more or less destroyed; the media contains vessels and is infiltrated, and it may be hypertrophic or atrophic. The thickened intima contains capillaries. The lumen becomes narrower and is usually eccentrically located. In general the alterations of the blood vessel walls depend on the nature of the tuberculous process. In the necrotic layer, destructive changes predominate. The media and even the hypertrophied intima are destroyed. The lumen is almost always obliterated before destruction occurs. Thrombosis is rare. Tubercle bacilli have never been found in the vessel walls, and caseation is rare.

MAX PINNER.

CHANGES IN THE OPTIC NERVE IN POSTVACCINAL ENCEPHALOMYELITIS. F. V. HERRENSCHWAND, Beitr. z. path. Anat. u. z. allg. Path. **87**:161, 1931.

In one case there was perineuritis, the infection apparently descending from the meninges. The inner layers of the dura showed perivascular lymphocytic infiltration and marked proliferation of fibrocytes with extension into the nerve. The second case presented an acute retrobulbar neuritis with changes similar to those found in the white matter of the brain. Numerous focal proliferations of glia, especially of Hortega microglia, were arranged perivascularly, especially about the central retinal vein at its point of entry into the optic nerve. Perifocal edema and marked degeneration of sheaths and axis cylinders were present. The meninges of the optic nerve were free. The similarity to the changes in myelitis, multiple sclerosis and epidemic encephalitis, except for the perivenous glia proliferation, is emphasized.

W. S. BOIKAN.

INTESTINAL CHANGES IN PELLAGRA. W. CEELEN, Beitr. z. path. Anat. u. z. allg. Path. **87**:488, 1931.

Ceelen's investigations of the gastro-intestinal tract in pellagra revealed severe enterocolitis of the small, and especially of the large, intestine which corresponded

to the microscopic observations of marked atrophy, superficial focal necrosis, dense infiltration and cystic glandular changes. These changes are considered the result of pellagra and not primary in the pathogenesis of the disease, which is essentially nutritive in origin.

W. S. Boikan.

Relation of Specific Granulations of Cells of Islands of Langerhans to Disturbances in Carbohydrate Metabolism. H. Hinteregger, Beitr. z. path. Anat. u. z. allg. Path. **87**:535, 1931.

In addition to the A and B cells described by Lane in the islands of Langerhans, the author describes a transitional cell between these two types. He considers the B cells the insulin-producing cells and believes that the A cells, the function of which is not known, may be precursors of the B cells, through the transitional cell stage. The transitional cells are not found in normal islands but in those which show a disturbed relationship of A and B cells. In the pancreas of pregnant guinea-pigs, there is a diminution of B cells with an increase of A cells. Animals given injections of insulin for a prolonged period show similar changes. Scorbutic animals show islands composed almost exclusively of B cells. In starved animals the islands either disappear or have an increased proportion of A cells.

W. S. Boikan.

Toxic Endocarditis. H. Willer, Centralbl. f. allg. Path. u. path. Anat. **56**: 1, 1932.

Willer raises the question of whether a pure toxic form of endocarditis can occur, concludes that this diagnosis may be accepted in the absence of bacterial infection and then offers an interesting observation in support of his ideas. The patient whom he observed was a 30 year old rachitic dwarf in whom, during her first pregnancy, in 1927, some symptoms of eclampsia developed. When he first observed her in 1931 she was five months pregnant, and had a blood pressure of 110 systolic and 70 diastolic and normal urine. When she was eight months pregnant eclampsia developed. She had a blood pressure of 180 systolic and 100 diastolic, many casts in the urine and large quantities of albumin. The patient died thirty hours after a cesarean section. Necropsy revealed: edema of the brain; thrombotic verrucous masses on the auricular surface of the mitral valve leaflets, surrounded by hemorrhagic regions; recent bronchopneumonia and hypostatic hyperemia of the lower lobes of both lungs; typical eclamptic changes in the liver, and acute degenerative as well as old fibrotic changes of the kidneys. Sterile cultures were obtained from the blood, spleen and heart valve leaflets. The only change in the body that cast doubt on the purely toxic character of the cardiac lesion was the bronchopneumonia. The author believes that endocarditis follows croupous pneumonia rather than bronchopneumonia. He also stresses the fact that the cardiac lesion in this case was older than the pneumonia. He concludes, therefore, that he dealt with a pure toxic endocarditis on an eclamptic-uremic basis.

George Rukstinat.

Gastric Mucosa in Ulcer and in Carcinoma. Horst Puchert, Virchows Arch. f. path. Anat. **280**:385, 1931.

Sixty resected stomachs with carcinoma or ulcer as well as a series of normal stomachs from autopsies were carefully studied histologically. In peptic ulcer of the stomach and duodenum there is an associated gastritis of a subacute type, verging on the chronic; this is not found in the fundus but is confined to the antrum. There is an increase in the size and number of the lymph follicles. There is very little epithelial metaplasia. In carcinoma there is a chronic pangastritis involving the entire mucous membrane. The lymph follicles are increased in number, but are small and show regressive changes. There is pronounced epithelial metaplasia. Bacteriologic examination in these cases gave negative results, leading to the conclusion that the toxic products of tissue necrosis are a factor in the production of the gastritis.

Perry J. Melnick.

SURFACE OVARIAN PREGNANCY AND ITS CLINICO-HISTOLOGIC DIAGNOSIS. GUSTAV GERSTEL, Virchows Arch. f. path. Anat. **280**:435, 1931.

The reported cases of ovarian pregnancy are reviewed. A case is reported which clinically appeared to be one of ruptured ectopic pregnancy. At operation the hemorrhage was found to come from one ovary. Microscopic examination revealed chorionic villi on the surface of a hemorrhagic mass which protruded from the ovary; these might have been easily overlooked. The possibility is considered that so-called idiopathic ovarian hemorrhages are really ovarian pregnancies which have not been recognized.

PERRY J. MELNICK.

MECHANISM AND SIGNIFICANCE OF THE CHANGES IN THE PULMONARY VESSELS IN INFLUENZAL PNEUMONIA. M. H. CORTEN, Virchows Arch. f. path. Anat. **280**:463, 1931.

In forty deaths from influenzal pneumonia in Hamburg during the winter of 1928 and 1929 the vascular changes in the lungs were found to be significant. In the early part of the epidemic the pneumonia was a hemorrhagic bronchopneumonia, later a serohemorrhagic lobar pneumonia, then a suppurative lobar pneumonia and finally an interstitial suppurative pneumonia. An apparently primary vascular injury was found to run a parallel course. At first there was necrosis restricted to the intima, with thrombosis and resulting hemorrhage. Later there was necrosis of the media; toward the end of the epidemic a suppurative arteritis developed and finally periarteritis, leading to an interstitial pneumonia. Similar vascular changes were observed in Berlin in 1930, and also during the pandemic of 1918.

PERRY J. MELNICK.

SO-CALLED PELIOSIS OF THE LIVER. W. GEISLER, Virchows Arch. f. path. Anat. **280**:565, 1931.

A review of the reported cases of so-called peliosis of the liver and two additional cases are presented. All except three doubtful cases were in tuberculous persons. The condition is a multiple telangiectasia of the central and sublobular veins of the liver and not multiple hemorrhages. It is occasionally associated with telangiectasia of the spleen. The etiologic factor is not considered to be tuberculotoxic, but a constitutional defect resulting in the angiectasis.

PERRY J. MELNICK.

CALCAREOUS CONCRETIONS OF THE SPLEEN. O. LUBARSCH, Virchows Arch. f. path. Anat. **286**:253, 1932.

The small calcified nodules sometimes seen in the spleen are usually phleboliths or calcified animal parasites. Lubarsch describes three spleens in which the nodules were situated in the malpighian bodies and were the result of an inflammatory reaction in the arteriole of the follicle.

O. T. SCHULTZ.

ACUTE PURULENT AORTITIS. O. AUERBACH, Virchows Arch. f. path. Anat. **286**: 268, 1932.

In a man, aged 81, acute suppurative inflammation of the arch of the aorta was secondary to cystitis and pyelonephritis. The ulcerative defect of the intima was covered by mural thrombus. In a woman, aged 34, the lesion of the aorta was of longer duration and was secondary to ulcerative endocarditis of the aortic valve. The process may lead to rupture or aneurysm of the aorta and hence may be confused with syphilis. In their histopathologic changes, healing lesions of longer duration may simulate syphilitic aortitis.

O. T. SCHULTZ.

FREQUENCY OF ASSOCIATION OF CHRONIC VALVULAR ENDOCARDITIS WITH ARTHRITIS DEFORMANS. N. GRZIMEK, Virchows Arch. f. path. Anat. **286**: 286, 1932.

A probable rheumatic origin of arthritis deformans may be inferred if this disease reveals an unusually high frequence of association with a common stigma of rheumatic infection, such as chronic valvular endocarditis. Of 520 knee joints examined at necropsy in an unselected series of necropsies of persons aged from 16 to 89, 91 revealed changes that were considered characteristic of arthritis deformans. Of the latter group, 42.8 per cent revealed healed or recurring valvular endocarditis. The latter condition was noted in only 17.9 per cent of the necropsies in which the knee joint was free from arthritis deformans.

O. T. SCHULTZ.

CHANGES IN THE COLLAGENOUS FIBRILS IN RHEUMATIC INFECTION AND IN OTHER INFLAMMATORY PROCESSES. F. SCHNOSNIG, Virchows Arch. f. path. Anat. **286**:291, 1932.

The earliest and most striking tissue reaction in rheumatic fever is the change that Klinge and his associates have termed fibrinoid degeneration of the ground substance of connective tissue. In this process the collagenous fibrils retain their identity, but become separated from each other and can be impregnated with silver by a modified Bielschowsky method. The present contribution presents the results of a study, by this method, of the tissues in a variety of inflammatory processes in which fibrinoid degeneration also occurs. These processes included streptococcic and staphylococcic tonsillar and peritonsillar phlegmonous inflammations, diphtheria, chronic gastric ulcer, tuberculosis and gumma. In all of these, changes in the ground substance of the collagenous tissue are associated with the development of an argentophil property by the collagen fibrils. In this respect there is no essential difference between the tissue reaction of rheumatic fever and the other inflammatory processes investigated. One difference, which may be of help in determining the rheumatic character of a lesion, is that the argentophil fibrils of the rheumatic lesion persist for a long time and throughout the various stages through which the lesion passes, whereas in the other processes the fibrils undergo necrosis and disappear.

O. T. SCHULTZ.

CHANGES IN THE SCIATIC NERVE IN RHEUMATIC INFECTION. S. KOEPPEN, Virchows Arch. f. path. Anat. **286**:303, 1932.

Histologic examination of both sciatic nerves was made in thirty-seven necropsies for the purpose of determining whether changes occur in rheumatic fever and whether in sciatica changes occur that might be interpreted as the result of rheumatic infection. The material consisted of eight cases of acute and subacute rheumatic fever, nine cases of healed rheumatic infection, four cases of clinical sciatica, six cases of sepsis and ten miscellaneous control cases. In acute and subacute rheumatic fever the walls of the small vessels of the nerve were swollen, and there were numerous small, perivascular lymphocytic infiltrations. In three cases of clinical chronic sciatica the presence of recurrent valvular endocarditis was accepted as evidence of previous rheumatic infection. In these the artery of the nerve of the clinically involved side revealed atherosclerotic changes; the intima was thickened and the media calcified. In a case of acute sciatica without rheumatic stigmas thrombosis of the femoral vein had led to thrombosis of the veins of the nerve. In the cases of healed rheumatic infection and in the remaining cases no alterations were detected in the sciatic nerve.

O. T. SCHULTZ.

CHANGES IN THE UPPER AIR PASSAGES AND ESOPHAGUS IN RHEUMATIC FEVER. D. SARAFOFF, Virchows Arch. f. path. Anat. **286**:314, 1932.

Gräff and Yoshitake have claimed that in rheumatic fever the infection enters by way of the tonsils and spreads downward through the lymphatics and tissue spaces into the organs of the neck. In seven unselected cases of acute and subacute rheumatic fever Sarafoff made a painstaking histologic study of the tissues of the pharynx, larynx, trachea and esophagus, down to the level of the bifurcation of the trachea. In six of the seven cases there were observed numerous characteristic focal rheumatic lesions, consisting in fibrinoid degeneration of the collagenous ground substance, cellular granulomas and scars. But the distribution of the lesions was not such as to uphold the view of Gräff and Yoshitake, and could be equally well interpreted as the result of widespread localization of the toxic-infectious agent by way of the blood stream.

O. T. SCHULTZ.

Microbiology and Parasitology

SEPTICEMIA IN THE NEW-BORN. ETHEL C. DUNHAM, Am. J. Dis. Child. **45**: 229, 1933.

Thirty-nine cases of septicemia in new-born infants are reported. The commonest causative organisms were the streptococcus, the staphylococcus and the colon bacillus. Septicemia caused by streptococcus was frequently accompanied by cutaneous infections, omphalitis, meningitis and peritonitis and invariably resulted fatally. In cases of septicemia caused by staphylococcus or by colon bacillus, jaundice was common and the spleen was frequently enlarged. Anemia was less common in septicemia due to staphylococcus than in that caused by streptococcus or by colon bacillus. Infection of the urinary tract was found only in cases of septicemia due to colon bacillus. Neither septicemia caused by staphylococcus nor colon bacillus was invariably fatal. The author concludes that septicemia is an important and relatively frequent cause of morbidity and mortality in the new-born.

RALPH FULLER.

"COMMON COLD" IN SPITSBERGEN. J. H. PAUL and H. L. FREESE, Am. J. Hyg. **17**:517, 1933.

A year's observation of respiratory diseases in the arctic mining town of Longyear City, Spitsbergen, indicates that the "common cold" is initiated by one or more specific, infective agents and that the disease is spread by direct contact. The period of incubation appeared to be about forty-eight hours. The clinical course of the disease varied in different persons who had presumably been exposed to the same "virus." Some persons seemed to have a complete immunity, while in others an immunity of short duration developed after an attack. This period was not shorter than twenty-three days in our series, and averaged seven weeks in the forty-nine persons who had had more than one attack at the time of our departure. The distribution of cases of the "common cold" by season is quite different from that reported for the temperate and tropical zones. The arrival of the first boat of the shipping season was followed by a sudden epidemic which involved almost the whole community in a short period of time. These epidemics are of annual occurrence. Our study indicated that an unfavorable environmental factor, such as a sudden drop in atmospheric temperature, is not necessary for the development of an epidemic. The study showed that the bacterial flora of the nasopharynx did not play any significant rôle in the initiation of the "common cold." Cultures from normal persons in Longyear City showed striking similarity to those obtained in the tropics and the temperate zone. The chief difference was that staphylococci and hemolytic streptococci were virtually absent in the population of Spitsbergen. This study confirms the fact that the fixed types of pneumococci and hemolytic streptococci are rarely encountered in isolated communities.

It also indicates that the various other groups of aerobic organisms isolated must be considered as normal inhabitants of the nasopharynx, since they occur in approximately equal percentages in normal throats in widely scattered geographical areas. It would be quite consistent with our observations to assume that the epidemic of "colds" described in this report was due to a filtrable virus of the type described by Dochez and his associates (*Lancet* **2**:547, 1931) and by Long and his associates (*J. Exper. Med.* **53**:447, 1931).

AUTHORS' SUMMARY.

EFFECT OF ENDAMOEBA HISTOLYTICA IN KITTENS. H. E. MELENEY and W. W. FRYE, Am. J. Hyg. **17**:637, 1933.

A study has been made of the relative pathogenicity for kittens of two strains of Endamoeba histolytica from the hill country of the Eastern Highland Rim of Tennessee and of three strains from the lowland of West Tennessee. Three hundred and sixty-four kittens were inoculated by rectum or by ileum with cultures of these strains. In the first series of rectal injections, performed when the strains had been in culture between 17 and 132 days, the lowland strains from acute cases produced a much higher incidence of infection than did the two hill strains. The lowland carrier strain produced an incidence of infection about equal to the chronic hill strain. The second series of rectal injections, performed with four of the strains when they had been in culture between 253 and 262 days, gave about the same incidence of infection with all strains. There was some increase with the hill carrier strain and a decrease with the two lowland strains from acute cases. Injection of cultures directly into the ileum gave a higher incidence of infection with all strains than injection by rectum. With each of the two hill strains a few kittens known to have been successfully infected showed no macroscopic lesions at autopsy, whereas none of the kittens successfully infected with the three lowland strains were without macroscopic lesions at autopsy. Most of the kittens successfully infected with the hill strains showed only a few small lesions in the colon, whereas most of those infected with the lowland strains showed moderate or intense pathologic processes. When the duration of the infection in each kitten is considered, foregoing differences in the pathologic process still hold true. The lesions produced by each of the lowland strains apparently progressed with greater rapidity than those produced by the hill strains. These observations seem to indicate that strains of E. histolytica from different localities may show differences in the incidence of infection and in the amount of pathologic change produced in experimental animals. A somewhat higher incidence of infection in kittens was obtained with culture transplants 2 or 3 days old than with older transplants.

AUTHORS' SUMMARY.

REMOVAL OF GALL BLADDER IN TYPHOID CARRIERS. H. F. SENFTNER and F. E. COUGHLIN, Am. J. Hyg. **17**:711, 1933.

Three hundred and sixty-eight chronic typhoid carriers have been discovered in upstate New York. The incidence of typhoid fever due to known carriers has been materially less subsequent to discovery as compared with the incidence prior to discovery. Removal of the gallbladder has resulted in the apparent cure of 59 per cent of those from whom required specimens have been submitted. The mortality among sixty-eight persons operated on was 14.7 per cent. If those in state institutions and those with acute gallbladder symptoms indicating operation are excluded, the mortality was 3.7 per cent. Sixty-eight per cent of those who survived the operation were apparently cured of the carrier condition. Removal of the gallbladder for the cure of chronic typhoid carriers should be advised only after careful consideration of the physical condition and age of the carrier and should not be advised unless preliminary duodenal specimens are positive.

AUTHORS' SUMMARY.

THE EFFECT OF IRRADIATED ERGOSTEROL ON CALCIFICATION OF TUBERCLES IN EXPERIMENTAL TUBERCULOSIS. M. JAMPOLIS and D. B. WITT, Am. J. M. Sc. **185**:338, 1933.

In two series of experiments intramuscular injections of a virulent culture of human tubercle bacilli were made into ten guinea-pigs, three serving as nontuberculous controls. In series B an attempt was made to simulate tuberculosis as it occurs in human beings. The procedure was the same as in series A, except that a preliminary injection of a known avirulent strain of human tubercle bacilli was given to all thirteen animals six weeks before the virulent culture was introduced. The effect of viosterol (administered orally) on the lesions produced was investigated. This demonstrated in a striking manner that the daily administration of viosterol in oil 1,000 X, in doses varying from 0.1 to 1 cc., causes deposition of calcium in the caseous tubercles in guinea-pigs. The blood of the animals so affected showed both hypercalcemia and hyperphosphatemia. There was no evidence of depletion of calcium in the roentgenograms of the bones. Spontaneous calcification did not occur in the tuberculous animals that received no viosterol. The most intense calcification was found in the lymph nodes and spleens of those tuberculous animals that were given the largest doses of viosterol. Deposits of calcium were noted only in the caseated areas. Undesirable calcification results if viosterol is given over a prolonged period in excessively large doses. In our investigation 0.2 cc. of viosterol in oil 1,000 X was administered daily for two months without any apparent harm. When continued for eighty-four days, undesirable calcification occurred. This dosage is equivalent to 6 cc. per kilogram of viosterol in oil 250 D. Calcification was present in the walls of the renal blood vessels and in the renal tubules of both the tuberculous and the nontuberculous animals that received daily amounts of viosterol in oil 1,000 X varying from 0.5 to 1 cc. for more than two months. No deposits of calcium were seen in the apparently normal portions of any of the other organs. The tuberculous animals that received the preliminary sensitizing injection did not show any definite calcification, possibly because the effect of viosterol is diminished in the presence of a fulminating secondary tuberculous process. The calcification of tubercles which was noted in this investigation is, in our opinion, not merely an expression of simple necrosis of the tissue but rather a reparative process. If it is permissible to calculate a human dosage of viosterol on a basis of weight, the maximum daily dosage given to our guinea-pigs corresponds to a dosage of 300 cc. of viosterol in oil 250 D, if given to a child weighing 22 pounds (10 Kg.). We refrain from making any recommendation concerning the clinical application of viosterol in tuberculosis because of possible renal damage. Future research may determine an optimum dosage which may have clinical value in certain types or stages of the disease.

AUTHORS' SUMMARY.

PRIMARY PERITONITIS COMPLICATING SCARLET FEVER. FERDINAND G. KOJIS and EDWARD J. MCCABE, Am. J. M. Sc. **185**:710, 1933.

A review of the literature shows that primary peritonitis complicating scarlet fever is a rare occurrence of grave prognostic importance. Three cases of this nature which developed in a series of 5,500 cases of scarlet fever occurring at the Willard Parker Hospital from 1928 to 1932 are reported. Most of the available evidence favors the blood stream as the route of transmission to the peritoneum, although many investigators favor the genital tract, in the female. A thick fibrinopurulent exudate covered the entire peritoneum in which the chief cell was the neutrophilic polymorphonuclear leukocyte. In two of the three cases culture of the peritoneal fluid yielded Streptococcus haemolyticus.

SANDER COHEN.

HERPETIC INFECTION OF THE CHORIO-ALLANTOIC MEMBRANE OF THE CHICK EMBRYO. J. R. DAWSON, JR., Am. J. Path. **9**:1, 1933.

The chorio-allantoic membranes of the chick embryo are susceptible to infection with a strain of herpes simplex virus which is innocuous to adult chickens of the

same breed. The microscopic lesions of these membranes are like those of herpetic lesions of mammals. A peculiar nuclear change in ectodermal cells is described, characterized by enormous enlargement of the nucleus, and by a partitioning of it by delicate trabeculae into compartments which are filled by minute, uniform and faintly stained basophilic granules.

AUTHOR'S SUMMARY.

CELLULAR INCLUSIONS IN LETHARGIC ENCEPHALITIS. J. R. DAWSON, JR., Am. J. Path. **9**:7, 1933.

A case of epidemic encephalitis is reported in which intranuclear and intracytoplasmic "inclusions" occur. It is suggested, on the basis of the presence of cellular inclusions, that this case of encephalitis may have been due to a cytotropic virus. Two other cases of encephalitis are mentioned in which no inclusions were found. It is further judged from an etiologic standpoint that epidemic encephalitis may not be a distinct entity. Inoculations into animals with material from each case induced no demonstrable infection.

AUTHOR'S SUMMARY.

LIVER ABSCESSES CAUSED BY A LEPTOTHRIX, WITH A REVIEW OF LEPTOTHRICAL INFECTION. P. N. HARRIS, Am. J. Path. **9**:71, 1933.

A summary of the literature pertaining to leptothrices pathogenic to man is presented. Report is made of a case of leptotrichosis in which multiple abscesses of the liver were formed, with rupture of one abscess into the base of the right lung and formation of an abscess of the lung, and rupture of another abscess in the left lobe of the liver, leading to the production of pericarditis. The organism was isolated in pure culture from the liver and successfully carried in vitro through many generations. No other organisms were present in the lesions. Experimental work with the organism showed it to be slightly pathogenic for rabbits and guinea-pigs. This organism has apparently never been previously encountered.

AUTHOR'S SUMMARY.

HISTOLOGICAL STUDY OF A CASE OF THE EASTERN TYPE OF ROCKY MOUNTAIN SPOTTED FEVER. P. N. HARRIS, Am. J. Path. **9**:91, 1933.

The occurrence of Rocky Mountain spotted fever in Tennessee and a histologic study of a fatal case are herewith reported. The occurrence of lesions of the brain in the Eastern form of Rocky Mountain spotted fever reported by Lillie is confirmed. Attention is called to a type of lesion of the brain which may prove to be diagnostic of the Eastern form of Rocky Mountain spotted fever.

AUTHOR'S SUMMARY.

THE MICROINCINERATION OF INTRANUCLEAR INCLUSIONS IN YELLOW FEVER. E. V. COWDRY, Am. J. Path. **9**:149, 1933.

In preparations of uninjured liver cells of the monkey made by micro-incineration, as specified in this article, the nuclear ash corresponds closely in position with materials seen in the fresh cells, as well as in fixed and stained preparations. The nucleolus, easily recognizable in fresh cells by its position, shape and refractive index, is found to be amphophilic in fixed and stained specimens and to yield a heavy, sharply localized ash after incineration. Chromatin, which is not visible as such in the still living cell but can be observed after fixation and staining in the form of basophilic substance scattered in the nucleoplasm and applied to the nuclear membrane, also leaves a mineral residue which is rather less dense. Marked alterations occur in nuclei reacting to the virus of yellow fever and in which nuclear inclusions are developing. The changes in size and shape of the nuclei, in the basophilic chromatin and in the nucleolus, described by Cowdry and Kitchen in stained preparations, can be followed with almost equal precision in the

incinerated specimens because parallel modifications occur in the mineral residue. But the nuclear inclusions, pathognomonic of the disease, although conspicuous features of the fresh and fixed and stained preparations, cannot be studied in incinerated specimens for they yield little or no ash. They therefore differ from the nucleoli and from basophilic chromatin in the same way that Scott observed in the case of nuclear inclusions caused by the action of the submaxillary virus in guinea-pigs.

AUTHOR'S SUMMARY.

VACCINE VIRUS PNEUMONIA IN ANIMALS. H. A. MCCORDOCK and R. S. MUCKENFUSS, Am. J. Path. **9**:221, 1933.

Vaccine virus injected into the lungs of rabbits, when strong, causes a hemorrhagic, edematous consolidation and irregular areas of necrosis; diluted, the virus causes interstitial infiltration with mononuclear cells. The first type of lesion is similar to the lesion found in the lungs of persons dying early in an attack of influenza. The second type of lesion resembles the interstitial cell infiltration of the bronchopneumonia in influenza, measles and whooping cough, with the bronchopneumonic exudate lacking, but this can be produced also by injecting bacteria after the introduction of the dilute vaccine virus. The authors regard interstitial bronchopneumonia as "the type reaction for the combination of a virus and bacteria, although in no sense specific for a particular virus or bacterium."

TUBERCULOSIS AND LEUKEMIA. R. H. JAFFE, Am. Rev. Tuberc. **27**:32, 1933.

The author describes three cases of myelogenous leukemia in which autopsy disclosed the activation of an old and apparently silent tuberculosis. The first patient died from an acinous nodose pulmonary tuberculosis which had markedly influenced the leukemia, improving the anemia and decreasing the number of white cells in the peripheral blood. Extramedullary myelopoiesis was restricted to the spleen. In the second case tuberculous peritonitis developed from tuberculous lesions in the peripancreatic lymph nodes. The tuberculosis had no effect on the leukemia. In these two instances the histologic picture of the tuberculous changes did not reveal any peculiarities, and typical epithelioid cell tubercles with giant cells were found. The third case showed a recent caseating tuberculosis of the right suprarenal, which was an accidental finding and was apparently secondary to the flaring up of an old focus in the right submaxillary lymph nodes. The suprarenal process showed a predominance of necrosis of the primary tissue and a lack of cellular response. There were no evidences that the leukemic cells took part on the defense reactions against the infection.

H. J. CORPER.

LOCALIZED EXPERIMENTAL TUBERCULOSIS OF THE LUNGS. ROBERT G. BLOCK, Am. Rev. Tuberc. **27**:143, 1933.

To produce localized pulmonary tuberculosis tubercle bacilli suspended in iodized oil are introduced into the trachea through an incision in the neck, a short needle on a tuberculin syringe being used with roentgenographic control of the localization of the infection. The method allows the production of localized primary tuberculous complexes with virulent bacilli. It can be used with advantage for experiments requiring slowly progressive lesions with late secondary involvement.

H. J. CORPER.

A COMPARISON OF CERTAIN MEDIUMS FOR THE CULTIVATION OF TUBERCLE BACILLI FROM SPUTUM. M. F. SHAFFER, Am. Rev. Tuberc. **27**:259, 1933.

The author studied six different mediums as to their relative value for the cultivation of the tubercle bacillus from sputum, following preliminary treatment with 6 per cent sulphuric acid according to a slightly modified Corper-Uyei method. The potato medium of Corper and Uyei yielded the largest number of positive reactions, with the Petragnani medium (of milk, potato and egg) yielding results

nearly as good. These two mediums were superior to the other four mediums tried as to the number of positive reactions. Lubenau's medium (of eggs) proved slightly superior to Dorset's (egg), Petroff's (veal infusion egg) and Sweany and Evanoff's (milk, veal and egg) mediums. Dissociation of the primary cultures into colonies resembling the so-called R and S types was noted particularly on Petroff's medium.

H. J. CORPER.

A COMPARISON OF TISSUE REACTIONS TO PULMONARY INFECTION WITH TUBERCLE BACILLI IN ANIMALS OF VARYING RESISTANCE. ARTHUR J. VORWALD, Am. Rev. Tuberc. **27**:270, 1933.

Tubercle bacilli of the human type in the proportion of 0.1 mg. per kilogram of body weight are injected intravenously into guinea-pigs, monkeys, dogs, rabbits, rats, cats and chickens. In all cases the pulmonary tissue, in contrast to the intrapulmonic lymphoid tissue, retained a major portion of intravenously injected tubercle bacilli, and the initial cellular reaction occurred at the point of lodgment of the organisms. The lymphoid structures of the lung were involved only secondarily. The susceptibility of the animals studied, as indicated by the measured extent of the individual cellular reactions, showed decided variations. The guinea-pig and the rabbit, although in the beginning responding with an equally intense reaction, ultimately differed greatly as to the amount of tuberculous tissue developed. The guinea-pig at one month proved to be a most susceptible animal and the rabbit a much more resistant one. The rat and the chicken, on the other hand, responding early with a reaction slightly less than that in the guinea-pig and rabbit, at one month showed decidedly more resistance. The monkey and dog, which at one day showed a minimal response, less than that in any of the aforementioned animals, at the final period proved to have less extensive tuberculous reaction than the guinea-pig, but much more than the rabbit, rat or chicken. The cat, the remaining animal of the series, reacted most sluggishly in the beginning, but, unlike the monkey and dog, in the final outcome proved a most resistant animal. The variations in susceptibility therefore did not parallel the intensity of the initial cellular reaction. In the guinea-pig, rabbit and rat the polymorphonuclear neutrophilic leukocyte played an important part in localizing the tubercle bacilli. Subsequently these leukocytes with their bacillary content were commonly phagocytosed by large mononuclear exudate cells. In the more mature reactions the mononuclear-exudate cell was the predominant type in all animals. No relation was detected between these mononuclear-exudate cells and the susceptibility of the individual species studied. There was an evident quantitative and also a qualitative difference in reactivity of the species—a quantitative one as shown by the difference in size of the cellular responses and a qualitative one in that in certain species polymorphonuclear leukocytes persisted in the responses throughout all periods. In other species these cells took little part in the later reactions, and in the chicken, a resistant animal, they were absent in the response at the one month period. No constant relationship was found between caseation and any particular type of cellular reaction.

H. J. CORPER.

HOT BATHS IN EXPERIMENTAL SYPHILIS OF RABBITS AND IN TRYPANOSOMIASIS OF RATS. JOHN A. KOLMER and ANNA M. RULE, Arch. Dermat. & Syph. **27**:660, 1933.

The authors infected rabbits intratesticularly with Spirochaeta pallida and four days afterward started daily immersion of the entire body, with the exception of the head, in water at 45 C. (113 F.) for twenty minutes. This resulted in prevention of testicular syphilis, and spirochetes could not be demonstrated in the inguinal lymphatic glands by animal inoculation. If the testicles were kept out of the water, syphilis developed in the usual way. They believe, therefore, that the sterilizing effects of hot baths are local rather than general. Similar immersion of rats infected with Trypanosoma equiperdum did not retard or prevent the development of fatal trypanosomiasis.

S. W. BECKER.

EXOGENOUS TUBERCULOUS INFECTION OF ADULTS. EUGENE L. OPIE and F. MAURICE MCPHEDRAN, Arch. Int. Med. **50**:945, 1932.

When roentgenographic methods are used for the recognition of tuberculous lesions of the lungs in spouses in contact with a tuberculous partner, exogenous infection of adults is clearly demonstrable. Husbands and wives in marital contact with tuberculosis under varying conditions are infected from five to nine times as often as persons with no known contact with the disease; husbands are infected oftener than wives. The frequency of infection in wives exposed to husbands with tubercle bacilli in the sputum was 35.5 per cent; in those exposed to husbands with no demonstrable tubercle bacilli, 22.9 per cent. The incidence of infection in husbands exposed to wives with open tuberculosis was 45.6 per cent, and when there were no tubercle bacilli in the sputum it was 35.9 per cent. When the incidence of latent apical tuberculosis in persons exposed to the disease in husband or wife is compared with that in husbands or wives with no known exposure to tuberculosis, the possibility that the difference has occurred by chance is negligible.

AUTHORS' SUMMARY.

BACTERIOLOGY OF ABSCESS OF THE LUNG AND METHODS FOR ITS STUDY. J. COHEN, Arch. Surg. **24**:171, 1932.

The subject of the bacterial flora of abscesses of the lung is reviewed. The technic of the cultivation of material from the abscesses is considered, with particular reference to anaerobiosis. Sixteen cases were investigated. Diphtheroids and "doubtful" anaerobic streptococci were present in each case. Bacterium melaninogenicum was next in frequency. A large variety of anaerobic bacilli were found. Definite conclusions as to the significance of the organisms were not reached.

N. ENZER.

MONOSPOROSIS (MADURA FOOT). M. GELLMAN and J. A. GAMMEL, Arch. Surg. **26**:295, 1933.

A third case of infection of the foot by Monosporium apiospermum in a native white American is described under the name of monosporosis. The clinical picture was that of mycetoma or madura foot.

PERLÈCHE. M. H. GOODMAN, Bull. Johns Hopkins Hosp. **51**:276, 1932.

A specific etiology of perlèche has not been determined. A case of chronic perlèche in an adult is reported, and also one of an acute type in a child. A survey of the literature and a cultural study of the two cases would suggest that perlèche may be primarily produced either by streptococci and staphylococci or by a fungus organism. However, there remains the possibility that an as yet undiscovered virus is the primary agent and that these organisms are secondary invaders. Histologic examination in the cases studied showed a chronic granuloma.

AUTHOR'S SUMMARY.

THE PATHOGENESIS OF TUBERCULOUS MENINGITIS. A. R. RICH and H. A. MCCORDOCK, Bull. Johns Hopkins Hosp. **52**:5, 1933.

Experimental and morphologic evidence is presented which demonstrates that diffuse tuberculous meningitis is not a direct and immediate result of hematogenous infection of the meninges. Miliary tuberculosis produces only rare, sparsely scattered tubercles in the meninges, not diffuse meningitis. Tuberculous meningitis has its origin in the discharge of bacilli into the cerebrospinal fluid from adjacent older caseous foci of the infection. Such discharging foci have been found, by careful search, in the substance of the brain or cord, in the meninges, in the bones encasing the central nervous system or in the choroid plexus in seventy-seven of

the eighty-two cases of meningitis in our series. In all except two of these seventy-seven cases, the source of the diffuse meningitis was situated in the substance of the central nervous system or in the meninges. In the five cases in which no discharging focus was found, the material for study was incomplete.

AUTHORS' SUMMARY.

EFFECT OF OLIVE AND COD LIVER OILS ON TUBERCULOSIS. L. NÈGRE, Ann. Inst. Pasteur **49**:319, 1932.

Guinea-pigs inoculated subcutaneously with bovine or human tubercle bacilli and treated by injections of olive oil showed more pronounced lesions than controls. These signs were apparent in certain larger nodes, in more numerous and more extended lesions in the spleen, and, in some cases, in involvements of the liver, lungs or bronchial nodes not marked in controls. The results with cod liver oil were somewhat similar. More numerous lesions were also observed in rabbits treated by injections of olive oil and cod liver oil. Sterilized and natural olive oils acted in the same manner.

M. S. MARSHALL.

EXPERIMENTAL MENINGEAL SPIROCHETOSIS. J. TROISIER, Ann. Inst. Pasteur **49**:343, 1932.

The subdural inoculation of Leptospira icterohaemorrhagiae produced in guinea-pigs acute fatal meningitis with or without icterus. There was a cellular reaction (mononuclears and polymorphonuclears) often accompanied by a local multiplication of spirochetes. Young rabbits gave similar responses, whereas in young dogs there developed either a benign curable meningitis appearing after six or eight days, with fever for a week following cure, or a malignant type with precocious cachexia and diffuse myoclonia. In both types of infection in the dogs there were a hypercytosis of the cephalorachidian fluid and an increase in albumin. In lower monkeys, when spirochetes had been injected into the cephalorachidian fluid, fever developed after a short period of incubation, and the animal became emaciated, without icterus. Thus, the reality of meningeal spirochetosis without icterus, as clinically observed in man, is proved with the spirochete of infectious jaundice.

M. S. MARSHALL.

NATURAL HISTORY OF TYPHUS. H. MOOSER, Arch. Inst. Pasteur de Tunis **21**:1, 1932.

Based on studies of the vectors and the behavior in animals of strains of the typhus virus, the question of the natural history of the viruses of the Old and New World is considered. A Tunis strain multipled in several varieties of fleas, but less regularly than a Mexican strain. Animals in a series in which the infection was started by bites of fleas showed fever and scrotal and cerebral lesions. Material from the latter showed no modification in the fever or period of incubation of inoculated animals. By rat-flea-rat passage most of the effects produced by Mexican strains were duplicated by Tunis strains. Differences seemed likely to be due to the hosts of the virus. Strains undergoing a rat-flea-rat passage during endemic periods (with low mortality) had qualities that were different from those of the man-flea-man strains of epidemic times (with high mortality). The possible significance of rats as reservoirs is considered great, and it is suggested that the Tunis virus, through longer adaptation, has lost some of the original properties manifested by the Mexican variety. Two addenda to the article make note of a report of a virus found in Greece which is similar to the American type, confirming the author's views, and of a report (April, 1932) of a Manchurian strain said to be specific, which the author criticizes as indicating no new strain.

M. S. MARSHALL.

COMMON ORIGIN OF TYPHUS AND OTHER EXANTHEMATIC FEVERS. CHARLES NICOLLE, Arch. Inst. Pasteur de Tunis **21**:32, 1932.

"To summarize in a phrase this long dissertation, we think, as does Moser, that these two typhus fevers (Old and New World) have a common origin; but we do not believe that one may transform itself into the other and that the hypothesis may be advanced that there exists only one typhus fever."

M. S. MARSHALL.

INFLAMMATORY EPETHELIAL REACTIONS OF ASCARIS. G. LÜBINSKY, Virchows Arch. f. path. Anat. **285**:691, 1932.

In higher animals study of epithelial reactions to inflammatory agents is complicated by the fact that epithelium is always associated with connective tissue, in which the most marked inflammatory reactions occur. Study of the reactions of epithelium alone is possible in those lower forms that contain no connective tissue, namely, hydroids and nematodes. In various species of Ascaris there occurs a disease known as dermomyositis. A study of this condition in the swine parasite (A. suum) is presented by the author. The body wall of the parasite consists of an outer chitinous cuticle, a syncytial epithelial hypodermis and a layer of longitudinal smooth muscle fibers. To injury or infection from without, the epithelium reacts by hypertrophy, hyperplasia and downgrowth into the underlying smooth muscle. The cuticle becomes thickened and isolates the invading micro-organism or the area of injured tissue. The isolating mass of cuticle is then sequestrated and cast off.

O. T. SCHULTZ.

VIOSTEROL IN TUBERCULOSIS. KÄTHE JÄGERMANN, Virchows Arch. f. path. Anat. **285**:764, 1932.

The oral administration of viosterol did not lead to calcification of caseous lesions or to increased connective tissue reaction about the tubercles in experimental tuberculosis of guinea-pigs. The histologic changes in the lungs of ten persons with pulmonary tuberculosis who had been treated with the vitamin preparation did not differ from those in eleven persons who had not received the oil. In the aortas of the patients who had been treated with irradiated oil there were observed changes that may have been due to the toxic action of the preparation.

O. T. SCHULTZ.

A CASE OF CONGENITAL TUBERCULOSIS. H. CHIARI, Virchows Arch. f. path. Anat. **285**:779, 1932.

Necropsy of an infant 13 weeks old confirmed the clinical diagnosis of general miliary tuberculosis and tuberculous meningitis. The tubercles, which were most numerous in the lungs, liver and spleen, were barely visible to the naked eye and were translucent. In the left lung was a partly calcified primary complex. In the liver were six partly calcified lesions, apparently as old as the primary focus in the lung. The lymph nodes at the hilus of the liver were caseous and partly calcified. The involvement of the liver and its nodes is also considered to have been a primary complex, as old as that of the lung. The author believes that infection occurred during the late intra-uterine period and led to primary involvement of the liver and the left lung.

O. T. SCHULTZ.

CULTIVATION OF TUBERCLE BACILLI FROM THE BLOOD AT NECROPSY. H. POPPER, F. BODART and W. SCHINDLER, Virchows Arch. f. path. Anat. **285**:789, 1932.

Cultivation of the cardiac blood at necropsy yielded tubercle bacilli in two of three early cases and in ten of eleven late cases of general tuberculosis. Eighteen of twenty cases of progressive pulmonary tuberculosis, in which the disease was

the cause of death, yielded positive results. In eight cases of progressive, nonfatal pulmonary tuberculosis and in thirty-three of stationary pulmonary tuberculosis, the results were negative. The bacilli were cultivated from the blood in a case of urogenital tuberculosis with a fatal outcome due to meningitis. Eight cases of organic tuberculosis, in which tuberculosis was not the cause of death, and three cases of polyserositis yielded negative results.

O. T. SCHULTZ.

Tumors

EXPERIMENTAL TOBACCO-CAUSED METAPLASIA OF THE GASTRIC MUCOSA OF THE DOG. A. MORATTI, Tumori **6**:101, 1932.

An attempt was made to reproduce smoker's plaques and "tobacco epitheliomas" in dogs and mice. A small portion of the stomach was isolated and repeatedly treated with tobacco fumes and a concentrated solution of nicotine. After two years typical plaques of cornified squamous epithelium could be observed in the mucous membrane of the isolated part of the stomach. No malignant growth was produced. The author considers the irritating effect of the nicotine as the cause of the metaplasia, and presumes that a second, internal factor is necessary for the development of a malignant growth.

E. VON HAAM.

LOCAL EFFECT OF INSULIN ON CANCER OF THE SKIN. S. F. GOMES, Tumori **6**:140, 1932.

The local application of insulin on ulcerated cancers of the skin produced healing of the ulcers and partial disappearance of the malignant growth. The epithelium which covered the treated ulcers was similar to normal squamous epithelium, and the neoplastic tissue on the margin of the ulcers underwent regressive, fibrous changes. In one case three fifths of the tumor disappeared under the treatment. Cancer of the skin seems to possess a specific sensibility for insulin; in this respect it differs from the medullary forms of carcinoma.

E. VON HAAM.

CATALYTIC ENZYMES OF THE BLOOD IN MALIGNANT TUMORS. A. LOREURI, Tumori **6**:201, 1932.

The author studied the volume of catalytic enzymes in the blood of patients with cancer before and after roentgen therapy. He found that there were fewer enzymes in the blood of patients with cancer than in the blood of controls. After roentgen therapy the volume of catalytic enzymes dropped considerably, probably because of the toxic effect of the destroyed tumor cells.

E. VON HAAM.

CHOLINE METABOLISM IN MICE WITH ADENOCARCINOMA. A. BOLAFFI, Tumori **6**:209, 1932.

The choline content of the growth and of the tissues of the animals inoculated with the tumor was studied and compared with that of normal controls. A steady increase of free choline was found in the growing tumor up to the twenty-fifth day of its growth. Thereafter the choline in the tumor tissue began to disappear, and only a slight increase could be found at the time of death. The choline curve of the animals with tumors showed a continuous decrease up to the time of death.

E. VON HAAM.

VALUE OF THE ASCHHEIM-ZONDEK REACTION IN THE DIAGNOSIS OF TUMORS. M. FERRO, Tumori **6**:314, 1932.

The author repeated the experiment of Engel, who reported the presence of secretion of the pituitary gland in the urine of patients with cancer. The technic of this test is the same as that of the Aschheim-Zondek test for pregnancy. In an examination of eighty patients with cancer the results were completely negative. The author therefore denies the value of this test in the diagnosis of cancer.

E. VON HAAM.

HISTOLOGIC CHANGES IN LYMPH GLANDS IN CANCER. N. MONTANINI, Tumori **6**:328, 1932.

The author studies the histologic picture of 800 lymph glands from 280 patients with cancer. Three groups of reaction are described. One group of glands showed an inflammatory reaction with hyperemia and hyperplasia of the lymphatic tissue. A second group showed marked hyperplasia of the reticulo-endothelial apparatus. In the third group marked fibrosis with atrophy of the glandular tissue was evident. Metastasis was found mainly in the third group. The first group showed a few malignant cells in the sinus, and the second group was always free from metastasis. The hyperplasia of the reticulo-endothelial cells in lymph glands of patients with cancer represents, therefore, a strong defensive reaction in the glands which protects them from invasion by the tumor cells.

E. VON HAAM.

REACTION OF BONE TISSUE FOLLOWING ADJACENT INOCULATION OF TUMORS. D. MUCCI, Tumori **6**:501, 1932.

In mice and adult rats the inoculation of sarcoma in parts near the skelton leads, first, to a proliferative reaction of the bone substance, followed by marked retrogressive changes. The proliferative reaction is produced by the periosteum of the bone and consists of callus-like formations, except that there is a remarkable disorganization in the histologic structure. The retrogressive changes affect the newly formed tissue as well as the preexisting osseous substance. The compact osseous substance is destroyed by lacunar reabsorption. The spongy bone substance undergoes fragmentation of the trabeculi. The appearance of multinucleated giant cells can be explained as a local reaction and can always be seen when the tumor penetrates the bone marrow. Finally, the picture of an osteoid sarcoma is produced.

E. VON HAAM.

THE CANCER CONSTITUTION. A. MORATTI, Tumori **6**:573, 1932.

The existence of a cancer constitution is an important discovery. The malignant tumor represents only a local symptom of a general metabolic disease of the organism. The experiments with tar cancer with different degrees of success in various animal groups make the existence of such a cancer constitution probable. The metabolic changes in patients with cancer have been thoroughly studied, and many interesting findings have been reported. Changes in the mechanism of the internal secretion and in the physicochemical reaction of the body fluids have been believed to be a sign of the existence of such a disposition. Cholesterol and carbohydrate metabolism, the relationship of calcium and potassium to tissue and body fluids and the albumin-globulin factor of the blood are found to undergo marked changes in patients with new growths. Warburg, Waterman and others in their fundamental experiments on the metabolism of the cancer cell are not able to explain fully the metabolic changes in the organism in the initial state of cancer. The existence of a constitution which forms a disposition to the development of cancer might also explain the frequent recidivation after surgical removal of a cancer, the multiplicity of malignant growths in the same person, as reported often in the literature, and the complicated mechanism of selective metastasis.

E. VON HAAM.

MICRODISSECTION STUDIES OF MALIGNANT AND NONMALIGNANT TISSUE CELLS. ROBERT CHAMBERS and R. J. LUDFORD, Arch. f. exper. Zellforsch. **12**:555, 1932.

On testing mammary gland and mammary carcinoma cells, embryo skin cells and cells from transplantable tar carcinoma, fibroblasts, sarcoma cells and macrophages according to the microdissection method, it was found that there are no differences in consistency between cancer cells and their nonmalignant prototypes. The two kinds of cells react to mechanical injury in the same manner. Puncture

of the nucleus always resulted in collapse and coagulation, followed by the death of the cell. Epidermal cells growing in sheets are firmly bound together, and the sheets may tear with no respect to cell boundaries. The epithelial cells of tar carcinoma adhere less firmly. Mammary cells, normal and cancerous, adhere, and, when separated, glutinous strands stretch between them. Fatty globules within the cytoplasm of mammary gland cells possess a membranous investment which can be wrinkled and torn with microneedles.

AUTHORS' SUMMARY.

MALIGNANT PINEALOMA AND MALIGNANT FETAL ADENOMA OF THE HYPOPHYSIS. E. KUX, Beitr. z. path. Anat. u. z. allg. Path. **87**:59, 1931.

A man, aged 22, had an infiltrating plum-sized pinealoma which showed cells of two types: small lymphocyte-like cells such as are normally present in the fetal and new-born pineal gland, and large cells, rich in cytoplasm, which probably developed from the former. Evidence of an internal secretory disturbance was lacking.

A man, aged 32, presented a 5 cm. suprasellar malignant fetal cell adenoma which compressed the base of the third ventricle. Clinically, there was evidence of local cranial changes plus mild acromegalial changes in the terminal phalanges. Hemorrhage into the tumor produced amaurosis and diabetes insipidus twenty-four hours before death from rupture into the ventricles.

W. S. BOIKAN.

MULTIPLE LIPOMAS OF THE SMALL BOWEL. A. ESSER, Centralbl. f. allg. Path. u. path. Anat. **55**:6, 1932.

Eight lipomas were found in 20 cm. of the jejunum of a 77 year old woman who had died of cardiac decompensation. The largest of these was the size of a cherry; the others were as large as a pea. They lay within the submucosa and were separated from the mucosa and muscularis by a layer of connective tissue. The bowel was involved in a marked chronic passive hyperemia, but this condition was lacking in the tumors, although the capsule of the largest of these was edematous. Except for the absence of rugae over the masses and occasional collections of small lymphocytes, the bowel in the vicinity of the tumors was unaltered.

GEORGE RUKSTINAT.

A HYPERNEPHROID ADENOMA OF THE LIVER WITH INCLUSIONS OF BONE. G. PATRASSI, Centralbl. f. allg. Path. u. path. Anat. **55**:37, 1932.

A friable tumor was found in the right lobe of the liver of a 67 year old man who had died of bronchopneumonia. The periphery of the tumor was composed of tissue resembling suprarenal cortex; its midzone was a voluminous mass of homogeneous hyaline material, and its center contained blood vessels, islands of bone marrow and cords of bone and osteoid tissue. Patrassi discusses the current theories of the origin of ectopic myeloid tissue and then contributes the following one: The vessels of the suprarenal medulla arise from the primordial kidney, and the branches of these vessels, which grow into the interrenal body, could in rare instances associate themselves with multipotent mesenchymal centers which later could produce bone marrow and bone. The presence of large blood lacunae and angiomatous regions in certain of these tumors seems to lend credence to the theory. No explanation is offered for the occurrence of such changes in the liver, however.

GEORGE RUKSTINAT.

A CASE OF MULTIPLE MYELOMA (PLASMOCYTOMA). J. B. PORCHOWNIK, Virchows Arch. f. path. Anat. **280**:534, 1931.

In the Russian literature only three cases of multiple myeloma have been reported. The author adds a fourth from the Government Roentgen-Radium Institute in Kiev, with a discussion of the pathology, clinical features, therapy and roentgenologic observations.

PERRY J. MELNICK.

TERATOID ABDOMINAL TUMORS OF THE FOWL. Ü. MASHAR, Virchows Arch. f. path. Anat. **285**:155, 1932.

The author describes two abdominal teratoid tumors of the fowl and tabulates eleven previously reported similar neoplasms. The tumors reached a relatively large size and exhibited variations in structure from well differentiated derivatives of the three germ layers to embryonal carcinomatous tissue. With one exception, the tabulated neoplasms occurred in cocks, chiefly in young ones. They arose in the testis, kidney or peritoneum. The tumor in a hen originated in the ovary. The author believes that the tumors originate in the celomic epithelium.

O. T. SCHULTZ.

OSTEOPLASTIC SECONDARY CARCINOMA OF THE LUNG. W. LAUBMANN, Virchows Arch. f. path. Anat. **285**:169, 1932.

In a case of inoperable carcinoma of the stomach in a man, aged 65, the lungs contained multiple metastases. Histologically, the metastases were composed of bone, osteoid tissue, cartilage and chondroid tissue. The tissues arose by metaplasia of the fibrous stroma of the metastases, brought about supposedly by the chemical stimulus of the tumor cells.

O. T. SCHULTZ.

INCIDENCE OF PRIMARY CARCINOMA OF THE LUNG AND BRONCHI. E. SIMMROSS, Virchows Arch. f. path. Anat. **285**:183, 1932.

The impression that the incidence of primary carcinoma of the lung and bronchi has increased in recent years was tested by an analytic study of the necropsy material in Gruber's institute in Göttingen. As the increase is supposed to have occurred since the war and the influenza pandemic of that time, the incidence of pulmonary carcinoma in 1,100 consecutive necropsies made from 1906 to 1912 is compared with that in an equal number of necropsies made from 1927 to 1931. Only necropsies of persons over 15 years of age were included. In the period from 1906 to 1912, the total number of cases of carcinoma was 194, or 17.63 per cent. There were 5 primary carcinomas of the lung, i. e., 0.45 per cent of the necropsies and 2.59 per cent of all the cases of carcinoma. In the period from 1927 to 1931, there were 173 cases of carcinoma, or 15.72 per cent. During this period there were 17 primary carcinomas of the lung; these constituted 1.55 per cent of the total necropsies and 9.83 per cent of all the carcinomas. The increase during the postwar period was progressive and reached its maximum in 1931, when 6, or 27.27 per cent, of 22 cases of carcinoma coming to necropsy represented primary pulmonary or bronchial carcinoma. The sex ratio in Simmross' series was 4.5 males to 1 female. In 900 cases tabulated from the literature, the ratio was 3.22 males to 1 female. In the Göttingen series, the right lung was involved in 12 cases, the left in 7 and both lungs in 3.

O. T. SCHULTZ.

PIGMENTED NEVI IN THE EPIDERMIS OF OVARIAN DERMOIDS. O. LUBARSCH, Virchows Arch. f. path. Anat. **285**:197, 1932.

Lubarsch refers to observations made originally twenty-six and twenty-four years ago to record the presence of pigmented nevi in the epidermis of ovarian dermoids of two women aged 80 and 61, respectively. The older woman had numerous pigmented and vascular nevi of the skin. Further search brought to light a vascular nevus of the dermoid epidermis. The senile character of the epidermis of the dermoid in this case and the loss of pigment from the hair of the dermoid, together with the nevi, favor the Marchand-Bonnet theory that the ovarian dermoid is derived from the same fertilized ovum that gives rise to the bearer of the dermoid, and that the dermoid is the single ovum twin of the woman who has the dermoid rather than her parthenogenetic offspring.

O. T. SCHULTZ.

HYPERNEPHROMA OF THE KIDNEY. L. PUHR, Virchows Arch. f. path. Anat. **285**:291, 1932.

Puhr describes eight tumors of the kidney belonging to the group usually termed hypernephroma, a designation to which the author objects. The presence of fat, glycogen and hemoglobin derivatives in the tumor cells is an expression of their specialized functional activity and is not due to regressive changes. These evidences of vital storage, together with the morphology of the tumor cells and their relation to the capillaries of the tumor, place the Grawitz tumor in the group of reticulo-endotheliomas.

O. T. SCHULTZ.

INCIDENCE OF TUMORS OF THE BRAIN. V. RUDERSHAUSEN, Virchows Arch. f. path. Anat. **285**:318, 1932.

Not the least interesting feature of this article is that it is based on the necropsy protocols from 1854 to 1931, inclusive, at the pathologic institute of the University of Heidelberg. Records for the years 1855 to 1862, inclusive, and 1864 are missing, but from 1865 on the series is complete. The total number of necropsies was 31,698. The total number of tumors of the brain was 546, or 1.72 per cent of all the necropsies. There were 444 (1.4 per cent of the total necropsies) primary and 102 secondary tumors of the brain. Of the primary tumors, 232 were classified as gliomas. The proportion of male to female patients was 5:4 for primary tumors, 4:3 for secondary tumors and 3:2 for gliomas. The largest number of primary tumors occurred in the fifth decade, and of the secondary tumors, in the sixth. The highest age incidence of glioma was from 45 to 50 for male patients and from 40 to 45 for female patients. The collective statistics of other observers are presented by the author.

O. T. SCHULTZ.

A CASE OF MULTIPLE TUMORS OF THE CENTRAL NERVOUS SYSTEM. RUTH KATZENSTEIN, Virchows Arch. f. path. Anat. **286**:42, 1932.

Necropsy of a man, aged 28, revealed multiple tumors of the dura of the brain and cord, bilateral tumors of the acusticus, multiple tumors of the posterior roots of the spinal nerves and multiple tumors of the substance of the cord from the cervical region to the cauda. The tumors of the cord had caused no symptoms. The symptoms, which had been slowly progressive for half a year, were due to one of the tumors of the cerebellopontile angle, for which operation was attempted. The tumors of the dura were fibro-endotheliomas, some of which contained calcified psammoma bodies. The tumors of the nerve roots were neurinomas and neurinofibromas. The interstitial tumors of the cord were differentiated gliomas. The central canal of the cord was dilated and surrounded by a zone of diffuse gliosis derived from incompletely differentiated ependymal cells that lined the canal. In the skin of the abdomen were three small fibromas. The case is called one of internal Recklinghausen's disease. The condition is held to be the result of embryonic maldevelopment.

O. T. SCHULTZ.

MAMMARY FIBRO-ADENOMA OF THE LABIUM MINUS. R. FRIEDEL, Virchows Arch. f. path. Anat. **286**:62, 1932.

A globular tumor nodule 3 cm. in diameter, covered externally by wrinkled skin, was attached by a long narrow pedicle to the labium minus of a woman aged 22. The growth had been present since the fourteenth year of her life. The histologic structure was that of a fibro-adenoma of the mammary gland. The tumor is believed to have arisen in a misplaced, supernumerary mass of mammary tissue.

O. T. SCHULTZ.

ENDOTHELIOMA OF THE PALPEBRAL CONJUNCTIVA. K. STOJALOWSKI and J. STASIŃSKA, Virchows Arch. f. path. Anat. **286**:70, 1932.

The authors present a brief description of a primary endothelioma of the palpebral conjunctiva in a youth aged 20. Endothelioma of the conjunctiva is rare.

O. T. SCHULTZ.

PRIMARY LYMPHOSARCOMA OF THE THYROID GLAND. C. O. RICE, Virchows Arch. f. path. Anat. **286**:457, 1932.

Rice, of Minneapolis, describes five primary lymphosarcomas of the thyroid gland, encountered in the surgical pathologic material in Wegelin's pathologic institute at Bern in the years from 1922 to 1929. The patients were women aged 50, 62, 67, 69 and 80, respectively. The tumor arises from the lymphoid follicles that are not infrequently seen in the thyroid gland.

O. T. SCHULTZ.

RETICULOSARCOMATOSIS. E. BENECKE, Virchows Arch. f. path. Anat. **286**:693, 1932.

The onset of illness in a boy, aged 4½ years, was insidious, with recurrent colicky pains in the upper part of the abdomen. A tumor could be felt in this region. The course of the illness was afebrile. The blood picture was unaltered except for moderate secondary anemia. Biopsy of the abdominal tumor left the clinical diagnosis undetermined as between diffuse reticulo-endotheliosis and primary localized reticulum cell sarcoma. Death occurred eight weeks after the onset of the illness. Autopsy revealed a large nodular tumor which arose from the retroperitoneal lymph nodes of the celiac region and which had invaded the pancreas, the left suprarenal gland and contiguous structures. The lymph nodes generally were enlarged, and in the neck the muscles were invaded by neoplastic tissue. There were multiple small nodules in the lungs and liver. The spleen was enlarged. The bone marrow was red and hyperplastic. Microscopically, the tissue of the main tumor, of the smaller tumor nodules and of the spleen, lymph nodes and bone marrow consisted of hyperplastic reticulum cells. Discussion is limited to the hyperplasias of the reticulo-endothelial system which may be grouped together under the term aleukemic reticulo-endotheliosis or reticulosis. In the majority of the reported cases the hyperplasia is secondary to septic infection. The neoplastic hyperplasias, the group in which Benecke's case belongs, may be diffuse and involve the entire reticulo-endothelial system, or they may occur as localized tumor formations with multiple metastases. In Benecke's case the gross anatomic picture was that of a large invasive tumor apparently with metastasis. Histologically, however, the picture was that of a disease of the entire reticulo-endothelial system. Direct transformation of Kupffer's cells to tumor cells was evident in the liver, and of reticulo-endothelial cells to tumor cells in the lymph nodes, spleen and bone marrow.

O. T. SCHULTZ.

RETICULUM CELL SARCOMA OF LYMPHOID TISSUE. F. ROULET, Virchows Arch. f. path. Anat. **286**:702, 1932.

In a previous issue of *Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medizin* (**277**:15, 1930) Roulet proposed the name retothelium for those cellular elements of the reticulo-endothelial system that lie directly on the reticulum of lymphoid tissues. Tumors derived from such cells he termed retothelial sarcomas, and claimed for them a relatively low grade of malignancy. In the present communication he describes eight cases of reticulum cell hyperplasia, some of which were more highly malignant than the previously described tumors, the latter being represented in the present series by two reticulum cell sarcomas of the axillary lymph nodes. The more highly malignant tumors had their origin in the tonsils or in pharyngeal lymphoid tissue. The series includes one case of diffuse, aleukemic, non-neoplastic hyperplasia of the reticulo-endothelial system and two cases in which there was diffuse hyperplasia as well as invasive neoplastic tumors with metastasis, the latter illustrating the transition from retotheliosis to retothelial sarcoma and retothelial sarcomatosis. One case of reticulum cell sarcoma is described, in which four years before death the blood picture was that of lymphatic leukemia. Under roentgen therapy the blood picture became normal, but there developed a mediastinal tumor of the character of a reticulum cell sarcoma, together with hyperplasia of the reticulum

cells of other lymph nodes. This case suggests the possibility of reversion of lymphoblastic tissue to the more primitive reticulum cell tissue. The author believes that it is necessary to separate the neoplastic and the non-neoplastic hyperplasias of reticulum cells from the neoplastic and the non-neoplastic hyperplasias of endothelial cells.

O. T. SCHULTZ.

Medicolegal Pathology

SUDDEN DEATH. T. H. B. BEDFORD, J. Path. & Bact. **36**:333, 1933.

One hundred and ninety-eight persons were found by the receiving officer to be dead on arrival at the hospital during twenty-one years, from 1910 to 1930. The relative importance of the various organs involved and the nature of the actual lesions have been investigated. The chief causes of death found were: disease of the coronary arteries, 80 cases; valvular disease of the heart, 35 cases; aneurysm of the aorta, 22 cases; disease of the respiratory organs, 19 cases, and cerebral hemorrhage, 15 cases; the coronary arteries were found diseased in 104 cases. In 15 cases postmortem examination failed to reveal any lesion which might have accounted for death. Attention has been drawn to the steady increase in the number of cases during the period covered by the review, and figures are presented which suggest that this increase is a general one, affecting to an equal degree the incidence of sudden death from all causes.

AUTHOR'S SUMMARY.

ARSENIC CONTENT OF THE ASHES OF HUMAN CADAVERS. H. JESSER and A. SCHREMPF, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:278, 1933.

The quantitative method of Ramberg (*Ztschr. f. Untersuch. d. Lebensmitt.* **52**: 448, 1926) for the determination of arsenic gives excellent results. In the ashes of a person who was treated with arsphenamine during his lifetime, the quantity of arsenic found was about the same as in ordinary cases of lethal arsenic poisoning. If a corpse which contained arsenic, either on account of arsenical medication or because of arsenical poisoning, was cremated, and subsequently an arsenic-free body was cremated in the same place, arsenic was found in the ashes of the latter. It was observed that the ashes of nine otherwise arsenic-free bodies cremated in succession showed the presence of arsenic, if an arsenic-containing body was first cremated in the same crematorium. These findings are of momentous medicolegal significance and should prevent erroneous interpretations.

E. L. MILOSLAVICH.

SUICIDE FOR INSURANCE PLANNED TO APPEAR AS A MURDER. A. MERKEL, Deutsche Ztschr. f. d. ges. gerichtl. Med. **20**:332, 1933.

A man was found shot dead in a wood under conditions indicating robbery and murder. However, from the position of the ejected shell and from a bullet scar on a nearby tree, it was decided that the man had committed suicide, holding the revolver in a peculiar position back of his occiput. The motive was economic distress and desire to provide for his family with the insurance money.

JACOB KLEIN.

MEDICOLEGAL ASPECTS OF DEATH FROM HEMATOPERICARDIUM WITH SPECIAL REFERENCE TO CARDIAC RUPTURE. B. LEWIN, Deutsche Ztschr. f. d. ges. gerichtl. Med. **21**:34, 1933.

In this thorough review of sudden death from hematopericardium, the author discusses the etiology, clinical manifestations and pathologic anatomy from the medicolegal point of view. Blood may enter the pericardium from rupture of the cardiac muscle, from a torn coronary vessel or from rupture of that part of the aorta within the pericardium. There is no case recorded in which fright or other emotional shock caused rupture in a normal heart. Cardiac rupture may be spontaneous or traumatic in origin. In the former instance the most common lesions are embolism, sclerosis or thrombosis of the coronary vessels, abscess of the

myocardium, brown atrophy, tuberculosis, syphilis and tumors. Traumatic rupture may be due to injury of the thorax sustained in boxing, falling from a height, crushing injuries, a kick by a horse and similar accidents. There may be such varied symptoms as severe precordial pain radiating to the left arm, cyanosis, restlessness, collapse, exhaustion and vomiting. From a medicolegal standpoint it is important to obtain a thorough history of the trauma with relation to the onset and course of the symptoms. It is essential to know whether or not the patient was ill before the trauma. Numerous clinical experiences and experiences at autopsy are briefly presented. The suggestion is made that surgical intervention may save the life of the patient in some instances. There is a comprehensive bibliography on this subject.

JACOB KLEIN.

INTRAVENOUS INJECTION OF METALLIC MERCURY. R. HEY, Deutsche Ztschr. f. d. ges. gerichtl. Med. **21**:257, 1933.

A 35 year old woman injected 2 cc. of metallic mercury into the cubital vein in an attempt at suicide. On the fourth day she suffered from diarrhea, palpitation and stomatitis. In the course of several weeks there was complete recovery from all symptoms. Seven years later the patient died of tuberculosis, in no way related to the mercurial intoxication. Anatomic study demonstrated metallic mercury in the liver cells, lungs and kidneys. No mercury was found in the central nervous system, pancreas, suprarenals, uterus or ovaries.

JACOB KLEIN.

DEATH WHILE BATHING IN COLD WATER. 1. RUDOLF KLOTZ, München. med. Wchnschr. **79**:1690, 1932. 2. KARL EISELBERG, München. med. Wchnschr. **79**:1691, 1932. 3. GRASSL, München. med. Wchnschr. **79**:1469, 1932. 4. J. P. ZUM BUSCH, Deutsche med. Wchnschr. **159**:15, 1933.

1. The sudden cooling of the surface of the body may be an important factor in causing death by drowning. This cooling causes a shift in the blood from the surface of the skin to the hypogastric and splanchnic region. The resulting dilatation of the visceral capillaries causes vertigo, weakness and collapse. Deaths from bathing in cold water during hot weather may be due to paralysis of the splanchnic capillaries from sudden cooling of the surface.

2. Unpleasant manifestations while bathing in cold water are often allergic reactions. In sensitive persons a cold bath may induce vertigo, weakness and even death by asphyxia.

3. The author himself noticed a sudden coldness in the feet while swimming in cold water on a hot day. On rubbing the cold areas large wheals formed. He felt ill, became faint and fell unconscious. After several minutes he recovered. A healthy, 50 year old woman, while bathing, had malaise, vomiting and vertigo. She might have drowned had not a bystander pulled her out. Her legs swelled from the ankles to the upper third of the thigh and were painful. A similar neuromuscular disturbance may cause "goose-flesh" and headaches after bathing. In more serious cases even death may result.

4. Some deaths during bathing may be due to allergy to cold. The author, although he has bathed in cold water since childhood, was sensitive to cold and suffered from paroxysmal sneezing and rhinorrhea. He could induce such an attack by sticking his foot out of the warm bed. In cold water his hands became swollen, red and itchy. On several occasions he experienced sudden weakness while swimming, so that he reached shore with the greatest difficulty and then collapsed. There would then be an eruption of giant urticaria about the joints. A similar reaction occurred once in a cold air bath. Such hypersensitiveness may occur only at times. Now, at the age of 65, the author swims in cold water without harmful symptoms. He considers the condition a form of allergy to cold.

JACOB KLEIN.

SPONTANEOUS RUPTURE OF THE AORTA. K. WOLFF, Virchows Arch. f. path. Anat. **289**:1, 1933.

The histologic examination of six examples of so-called spontaneous rupture of the aorta confirmed the observations of Erdheim and others that rupture occurs through severely damaged areas of the media. In such areas, which appear as bands or streaks in sections, the media is degenerated, structureless and devoid of nuclei. Masses of mucoid material are seen in the degenerated areas. Similar lesions were seen in the aorta at points distant from the rupture, in the pulmonary artery, and in the carotid, iliac and femoral arteries, leading Wolff to suggest that the process is a systemic disease of the arteries, the first manifestation of which is focal destruction of the elastic tissue. The degenerative lesions begin about the vasa vasorum, hence Wolff postulates a noxious agent, probably chemical in nature, that reaches the arterial wall by way of the nutrient vessels. Increased blood pressure is an added factor in the production of the lesions and in the rupture. In one case the degenerative process of the media of the aorta had led to marked proliferation of a type that Wolff terms re-formation of the wall, since connective and elastic tissue and smooth muscle all took part in the proliferative process. The article ends with a tabulation of nineteen cases of spontaneous rupture of the aorta, including thirteen previously reported cases and Wolff's six.

O. T. SCHULTZ.

NECROSIS AND HEMORRHAGE IN TUMORS OF THE BRAIN. B. KARITZKY, Virchows Arch. f. path. Anat. **289**:83, 1933.

A medicolegal case raised the question whether the necrosis and hemorrhage noted in a tumor of the brain were the result of an electric shock that the victim had sustained. To furnish information for the solution of this question, the author examined 115 gliomas and 18 ganglioneuromas of the brain, the material having been collected since 1912 in Schridde's pathologic and medicolegal institute at Dortmund. Macroscopically evident necrosis was noted in 80 per cent of the tumors, and hemorrhage in 76 per cent. Necrosis is the result of the cellular character of the tumors and is brought about by degenerative changes in the vessels of the tumor; necrosis was not observed in denser, acellular tumors. Hemorrhage is secondary to necrosis. In only one of the tumors examined had there been fatal hemorrhage without necrosis, due to external action.

O. T. SCHULTZ.

Society Transactions

INTERNATIONAL ASSOCIATION OF MEDICAL MUSEUMS, AMERICAN AND CANADIAN SECTION

Twenty-Sixth Annual Meeting, Washington, D. C., May 8, 1933

GEORGE R. CALLENDER, *Fort Sam Houston, Texas, President, in the Chair*

THE MUSEUM OF PATHOLOGY OF THE UNIVERSITY OF TORONTO. Presented by T. H. BELT.

This museum has been developed for teaching purposes alone and has been arranged somewhat differently from museums in general in that the total collection, which comprises about three thousand mounted specimens, is divided into ten groups, each of which is housed in a separate room. One of these rooms is devoted to the teaching of general pathology, and the other nine to specimens illustrating the various aspects of special pathology.

A NEW FORM OF MUSEUM CATALOG. WILLIAM BOYD, Winnipeg, Canada.

A method was described which has proved to be a satisfactory solution of the cataloging problem. This is primarily a teaching collection of about fifteen hundred specimens extensively used by students of pathology for reading purposes. The specimens are mounted under watch-glass and are placed in three tiers on either side of a home-made fixture similar to a magazine desk in a library, which replaces the ordinary museum case. The distinctive feature is that along the entire length of the fixture and attached to the lowest tier there runs a thin board, 11 cm. in depth, which is set 8 mm. from the stand; this provides a narrow box which is divided by transverse partitions corresponding in size with the largest of the watch-glass specimens. This holds a stout card 5 by 7 inches on which can be typed the description of the specimen (gross and microscopic), summary of the clinical history and observations at autopsy. Both sides of the card are used, and more than one card may be employed. carrying, if desired, a photomicrograph and reduced roentgenogram on the back. Three of these cards are contained in each receptacle, corresponding to the three specimens immediately above on the stand. The specimens are not labeled, but each carries the number of its corresponding card, thus stimulating the student to make his own diagnosis. Each fixture consists of a 12 foot stand carrying eighty-four specimens, and under this arrangement from thirty to forty students can work with comfort at one time without interruption.

THE SELECTION OF A LIBRARY OF PATHOLOGY. ROBERT A. MOORE, Cleveland.

The abstracts in five volumes each of the ARCHIVES OF PATHOLOGY and the *Centralblatt für allgemeine Pathologie und pathologische Anatomie* were indexed on the assumption that the journal most frequently abstracted is the most valuable journal. Twenty-two journals carried 50 per cent of the articles abstracted in these ten volumes. The remaining 50 per cent appeared in over two hundred journals. Journals of pathology carried 41 per cent of the literature, journals of other medical specialties 48 per cent and other journals and transactions 11 per cent. The cost per page showed that the German journals average 3.5 cents a page as compared with about 1 cent a page or less for the English, French and American journals.

DISCUSSION

GEORGE R. CALLENDER: It is gratifying that the comparative expense of the available literature has been presented in concrete form.

VICTOR C. JACOBSEN: Such an investigation is extremely helpful, especially during these times of financial stringency and practically universal reduction of budgets. The situation is especially acute in regard to German publications, the high price of which has become a serious matter. A closer collaboration between the work of the anatomic and pathologic departments is also needed on both economic and scientific grounds.

A PROCESS OF EMBALMING, AND SOME NOTES ON DIDACTIC ANATOMIC TECHNOLOGY. PEDRO ARA, Professor of Systematic Anatomy, Madrid, Spain.

The speaker, who had come from Spain especially for the purpose of attending this meeting, presented a truly remarkable specimen consisting of the upper half of the thorax and head of an old monk, preserved without any shrinkage to such a high degree of perfection that the physiognomy and even the expression were retained in an extraordinary lifelike manner. The technic followed was essentially a simple process of paraffinization similar to that used in the impregnation of material for histologic purposes; therefore a good preliminary fixation, absolute dehydration, etc., formed the basis of the method employed.

1. IMPROVED TECHNIC IN THE MAKING OF GLASS FRAMES FOR MOUNTING SPECIMENS IN CORRECT ANATOMIC POSITION. 2. THE DRY MOUNTING OF CALCULI. 3. A HANDY MICROSCOPE LIGHT. JOSEPH GIROUX, Montreal, Canada.

1. Special devices in the making of glass frames to secure greater solidity by means of additional supports of the frame and to obtain greater facility in workmanship with the blowpipe and otherwise are described. 2. Calculi are best preserved when they are placed in a dilute solution of formaldehyde (1:10), washed in running water for twenty-four hours, passed through 98 per cent alcohol to restore their color, and finally, when perfectly dry, painted with a hard photographic varnish. Sectioning, when required, is done under water by means of a small jeweller's saw-blade with very fine teeth on both edges, the cut surface being polished on a piece of glass covered with fine emery powder and water. 3. An efficient microscope lamp may be made from a 4 pound potassium acetate tin with a hole cut in one side to expose a 500 cc. flask of distilled water fastened within, and supplied with an electric light bulb, two mirrors suitably adjusted for reflection and ventilation slits.

METHODS OF MOUNTING GROSS SPECIMENS OF EYES AT THE ARMY MEDICAL MUSEUM. HELENOR CAMPBELL WILDER, Washington, D. C.

Specimens fixed in Kaiserling's solution are mounted on sheet celluloid with a solution of celluloid in acetone. Celloidin blocks, from which sections have been cut, are partially dehydrated in 95 per cent alcohol, stuck to the faces of small museum jars with thin celloidin and mounted in equal parts of absolute alcohol and cedar oil. Both types of mounts are sealed with Duco household cement.

A SIMPLIFIED GELATIN METHOD FOR MOUNTING MUSEUM SPECIMENS. N. S. SAHASRABUDHE, Nagpur, India.

Preliminary fixation is carried out by injection of a dilute solution of formaldehyde (1:20) into the carotid or femoral artery. Sections taken are preserved in a modified Jore's solution, and the gelatin (French, gold label) is mixed with water in the proportion of 1:10, 50 cc. of a solution of formaldehyde being added thereafter to every 500 cc. of the gelatin mass. For mounting, the jar is held on the slant and the specimen arranged on one surface; liquid gelatin is then introduced

to cover it and is allowed to congeal, the jar being placed within an ice jacket for five minutes for this purpose. After it is solidified, the remaining space in the jar is filled with a dilute solution of formaldehyde in distilled water and sealed.

CURRENT ACTIVITIES AT THE ARMY MEDICAL MUSEUM. VIRGIL H. CORNELL, Washington, D. C.

These include studies of the functioning of the bladder and the eye, lymphatic tumor registries, the work done by the museum as the central laboratory of pathology for the army, the development of three-color photography, rearrangement of exhibits and improvement of lighting in the museum, various exhibits presented during the past year by the museum and the file of results of original research.

DISCUSSION

V. C. JACOBSEN: The Army Medical Museum has done excellent work in assembling material in its tumor and other registries. From time to time there arise problems in pathology promulgated by some person which require a great deal more investigation to evaluate properly. Thus the work being done by Cushing on changes in the hypophysis may revolutionize the pathology of eclampsia. I consider it essential to examine the hypophysis carefully in all cases of eclampsia. No one person will obtain much material of this kind, so that it is important to assemble the specimens at one point. I am wondering whether the Army Medical Museum might at some time attempt to collect such hypophyses. I do not know any better place.

HOWARD T. KARSNER: It seems to me that a paper of this sort should not go by without adequate discussion. It represents what can be done by the United States Army Medical Corps in the face of the most distressing conditions. I think that as an association we should feel a great sense of pride in its accomplishments. As Dr. Jacobsen has said, many things might be utilized in the way of research. The state of New York has been trying to determine the standards of surgical pathologists, and examinations are being conducted which are of the utmost value. It is interesting to know the results of this activity; the subject may at some time reach national proportions. It is to be hoped that the United States will be able to maintain the high standards of the Army Medical Corps.

GEORGE R. CALLENDER: The Army Medical Museum is the national medical museum, and the pathologists of this country have been of assistance. In the line of surgical research we have housed the material of a great many investigators, consisting of reprints, slides and many specimens. Every year more and more is added to this wealth of material. I should like to remind the members that the Department for the Preservation of Objective Results of Medical Research is essentially a part of the International Association of Medical Museums, the material being housed at the Army Medical Museum by permission of the Surgeon-General in response to the request of the council of this association and as a result of its organization.

AN INEXPENSIVE METHOD OF DEMONSTRATING HISTOLOGIC SLIDES TO SMALL GROUPS. WALLACE J. PLUMPTON, Montreal, Canada.

A simple apparatus was demonstrated which is quickly set up by placing a microscope in front of an ordinary lantern slide projector and removing the eye piece of the microscope.

SANTALIN, A SELECTIVE STAIN FOR THE FATTY ACID CRYSTALS IN FAT NECROSIS. W. F. SHERIDAN, Washington, D. C.

A Simple Knife Sharpener. William Boyd, Winnipeg, Canada.

A knife sharpener, similar in principle to the Schmidt microtome knife sharpener, can easily be made by the hospital mechanic at a trifling cost. It consists of a knife carrier which slides on ball bearings on a base of plate glass, the knife moving on a smaller plate of ground glass. Abrasives are poured over the latter, the most useful being fine emery and white rouge. With this simple device a microtome knife can be given a perfect edge by any technician.

A Simple Silver Technic for Nerves and Tactile Corpuscles in Pigmented Moles. George F. Laidlaw, New York.

Nerve fibers in pigmented moles were shown by a rapid and simple silver stain based on that of Gross and Bielschowsky. Some nerves terminate in tiny bulbs on the nevus cells as they do on the tactile cells of the epidermis and the hair follicles. Other nerves have thick sheathing of Schwann cells. The stain confirms Masson's assertion that pigmented moles are neuromas and schwannomas of the sensory nerves of the skin.

A Case of Hemorrhage from the Nipple Due to a Benign Intraductal Polyp. Helen Ingleby, Philadelphia.

A married woman, aged 32, had a brownish watery discharge from the nipple two years before operation. One year later a tumor was noticed, and six weeks before admission to the hospital she had bleeding from the nipple, lasting for ten days. A benign intraductal polyp was found which had the structure of a fibroadenoma. The ducts in the adenoma resembled those of the surrounding breast and were in the late premenstrual phase. The mechanism of formation of this type of tumor was discussed.

A Case of Primary Calcification in Muscle Fibers of the Heart. Dora Deng, Shanghai, China.

A white woman, aged 28, died of chronic glomerular nephritis. At autopsy numerous calcified plaques were found in all systemic arteries and three small calcified nodules in the wall of the left ventricle. On the basis of Rabl's experiment and Wells' and Kuttner's hypothesis, the extensive deposits of calcium were explained as due to phosphoric acid retention resulting from renal lesions and to the concentration of carbon dioxide in the blood at those particular sites.

Aortic Stenosis: A Differential Study in Calcified Bicuspid Valves Between Those of Congenital or Inflammatory Origin. Louis F. Bishop, New York, and Max Trubek.

With fusion and calcification of the aortic cusps it was often difficult to decide on gross examination whether we were dealing with an old inflammatory process or with a congenitally bicuspid valve with subsequent calcification. By the method described by Lewis and Grant (1923), serial sections stained for elastic and connective tissue were cut through the ridge or raphe dividing the conjoint cusp. A normal valve and a typical congenital raphe were similarly sectioned for comparison with the pathologic material. The method proved a satisfactory aid in most of the cases.

DISCUSSION

M. E. Abbott: This is a very valuable contribution. Lewis and Grant first established a differential microscopic picture of the congenital as compared with the acquired lesion, but stated that additional studies on the architecture of bicuspid aortic valves were desirable in order to verify their conclusions, which were necessarily drawn from a relatively small number of cases. Dr. Bishop has done this and has also delineated the histologic features of the two types of cases clearly.

CONGENITAL ANEURYSM OF THE INTERVENTRICULAR SEPTUM. ERIC MASSIG, Toronto, Canada.

This case was of a man, 49 years of age, who died of coronary disease. An unrelated finding at autopsy was a small aneurysm of the membranous portion of the interventricular septum. It extended from the left ventricular cavity into the medial leaflet of the tricuspid valve. There were no signs of acute or chronic inflammatory changes about the aneurysm.

DISCUSSION

ROBERT A. MOORE: Are there any criteria by which differentiation of a congenital origin can be made?

T. H. BELT: The absence of any sign of endocarditis is in favor of an anomaly.

M. E. ABBOTT: The seat of the aneurysm in this case is characteristic of a congenital lesion.

CONGENITAL ANOMALIES OF THE CORONARY ARTERIES: REPORT OF AN UNUSUAL CASE ASSOCIATED WITH CARDIAC HYPERTROPHY. EDWARD F. BLAND, PAUL D. WHITE and JOSEPH GARLAND, Boston.

In a boy dying at the age of 3 months, abnormal origin of the left coronary artery from the pulmonary artery was found associated with marked enlargement of the heart (due to hypertrophy and dilatation of the left ventricle), together with extensive degenerative changes in the ventricular wall supplied by the malposed vessel. In view of these findings, it is probable that the paroxysmal attacks of acute discomfort precipitated by exertion and associated with profound vasomotor collapse occurring in this infant were angina pectoris. The electrocardiographic picture was similar to that seen in adults with serious coronary disease. In the few recorded cases (eight in addition to our own) of this rare anomaly a characteristic pathologic picture has resulted. Death within the first year has been the rule. Two of the cases have been exceptional.

DISCUSSION

V. C. JACOBSEN: This work is particularly valuable in that it shows how the heart reacts to what is essentially occlusion of one main coronary artery. Some nourishment from a venous supply is possible, and to a certain extent this has occurred in this case. Coronary arteriosclerosis in older patients has been cited, with no particular change in the myocardium and without the history of a definite cardiac attack even in the presence of marked narrowing of the coronary vessels. In such cases the myocardium must have been nourished by other vessels such as the thebesian vein. No hard and fast rule can be laid down as to what to expect when one coronary artery (and not both) is occluded.

M. E. ABBOTT: Dr. White's presentation of the clinicopathologic findings is valuable. This is the first case of anomalous origin of the left coronary from the pulmonary artery in which an electrocardiogram has been taken, linking up the changes that must have occurred in the myocardium with the resultant functional disturbance.

P. D. WHITE: Electrocardiograms have been taken in two cases of idiopathic hypertrophy of the heart in infancy.

NEW YORK PATHOLOGICAL SOCIETY

Regular Monthly Meeting, May 26, 1933

PAUL KLEMPERER, *President, in the Chair*

MULTIPLE SACCULAR ANEURYSMS OF THE CEREBRAL ARTERIES: RUPTURE INTO THE SUBDURAL SPACE. MILTON HELPERN.

A 51 year old white laborer was found dead in bed. Because of a recent injury to the hand and to the forehead the cause of death was investigated by the medical examiner's office. At autopsy, the body was poorly nourished. Except for a large fatty liver and an inelastic but smooth aorta, the organs were not unusual. The skull was uninjured.

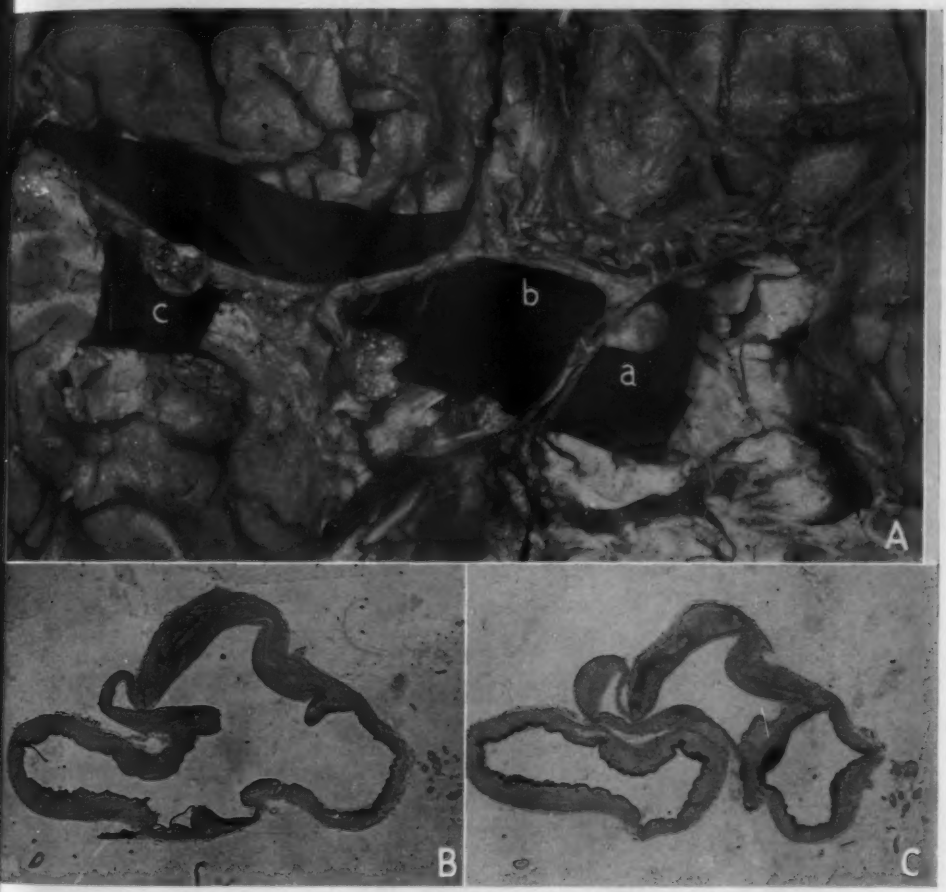
A large, fresh, subdural hemorrhage weighing more than 85 Gm. covered the base of the skull and extended upward over both cerebral hemispheres. The blood was not adherent to the surface of the arachnoid or to the smooth inner surface of the dura. The communicating veins between the pia and the dural sinuses were not torn, and the surface of the brain was intact. A small, thin area of subarachnoid hemorrhage localized over the anterio-inferior portion of the left temporal lobe was continuous in the fissure of Sylvius with a small collection of soft, clotted blood overlying a saccular aneurysm 6 mm. in diameter which arose from the superior and lateral wall of the commencement of the left middle cerebral artery just beyond the origin of the posterior communicating branch (fig., *a*). The aneurysm was situated above and lateral to the internal carotid artery at the point where that vessel passes out of the subdural space into the subarachnoid space to continue as the middle cerebral artery. When the brain was removed, the carotid stump was cut close to the circle of Willis, probably through the site of the rupture of the aneurysm, which was not found elsewhere. The rupture at the point of transition from the internal carotid to the middle cerebral artery explained the large subdural hemorrhage and only slight localized subarachnoid hemorrhage.

Two additional saccular aneurysms were found arising from the cerebral arteries. Halfway along the left anterior cerebral artery, the vessel bifurcated into two closely placed parallel branches of slightly unequal caliber which reunited in the region of the anterior communicating branch. The second aneurysm, 1.5 mm. in diameter, arose at the point of bifurcation and was wedged between the two branches, its inferior surface bulging as a small translucent nodule (fig., *b*). The third aneurysm was in the angle of the first bifurcation of the right middle cerebral artery (fig., *c*). In size and structure it was similar to the first aneurysm described. The basilar and carotid arteries were slightly thickened. No lesions were found in the brain substance, which on chemical examination contained a moderate amount of ethyl alcohol.

The large aneurysm on the left middle cerebral artery and the small one on the left anterior communicating artery were sectioned for histologic examination. Both occurred at a bifurcation; the former, where the internal carotid became the middle cerebral artery after giving off the posterior communicating branch, and the latter, at the unusual bifurcation of the anterior cerebral artery in the middle of its course. Weigert's elastic tissue stain and van Gieson's stain revealed an aneurysmal wall almost devoid of internal elastica and muscularis and composed of a slightly thickened continuation of incomplete intima and adventitia. The wall of the larger aneurysm was considerably thinner than that of the smaller one on the anterior cerebral artery, which is shown in the figure, *B* representing the origin at the point of bifurcation and *C*, a few sections anteriorly, representing the aneurysm wedged between the two branches. The almost complete disappearance of internal elastica in the aneurysm is easily made out.

The aneurysms were saccular and obviously not due to arteriosclerosis, trauma, syphilis or other inflammation. Their occurrence at the bifurcation of the cerebral

arteries and their multiplicity, size and histologic structure place them in the group described by Forbus (Miliary Aneurysms of the Cerebral Arteries, *Bull. Johns Hopkins Hosp.* **47**:239, 1930). He expressed the belief that the lesions are acquired, arising from a combination of focal weakness in the vessel wall, as a result of a congenital defect in the muscularis at points of bifurcation, and subsequent degeneration of the internal elastica due to continued overstretching by the force of blood pressure. Rupture of cerebral aneurysms into the subdural space with an absence of massive subarachnoid hemorrhage is unusual, in this instance



A, the base of the brain. Multiple saccular aneurysms are seen at *a*, *b* and *c*, arising at points of bifurcation of the cerebral arteries. The temporal lobes have been removed. There is no subarachnoid hemorrhage. Black paper has been inserted behind the vessels for contrast. *B* and *C*, sections through the left anterior cerebral artery at the site of the aneurysm seen in *A* at *b*; Weigert's elastica stain. *B* shows the aneurysm devoid of elastica and muscularis, arising at the bifurcation; *C*, the aneurysm a few sections farther on, wedged between the two branches.

probably occurring at the point where the internal carotid artery emerged from the subdural into the subarachnoid space to continue as the left middle cerebral artery. In a clinical case of this type, the diagnosis would be obscured by the

obtaining of a clear spinal fluid on lumbar puncture instead of the usual bloody type. These aneurysms, judging from their size, should not be designated as miliary.

METASTATIC CARCINOMA OF THE SPLEEN. ELMA BARANY and ANGELO M. SALA.

As metastatic carcinoma of the spleen is rare, the two cases presented here are of interest.

CASE 1.—A woman, aged 68, was admitted to the New York City Cancer Institute Hospital on Sept. 19, 1932, with pain in the abdomen of four months' duration. There were a firm mass in the right axilla, a few subcutaneous nodules around the umbilicus and a fixed, hard mass in the pelvis, pushing the uterus to the left. A clinical diagnosis of carcinoma of the ovaries with metastases to the umbilicus and right axilla was made. The patient died on December 27. Autopsy confirmed the diagnosis of carcinoma of the ovaries with general carcinomatosis. There were metastases to the liver and to the spleen, which presented a metastatic deposit in its parenchyma, about 1 cm. in diameter, extending nearly to the surface. Histologically, both ovaries and all the metastatic deposits showed adenocarcinoma.

CASE 2.—A man, aged 72, was admitted to the New York City Cancer Institute Hospital on Aug. 8, 1932. Prostatectomy had been performed in 1931, and the prostate proved to be malignant. Physical examination showed nothing of importance except, on rectal examination, a nodular mass in the prostatic area. A diagnosis of carcinoma of the prostate was made, and high voltage roentgen treatment was administered. The patient died on Jan. 9, 1933. Postmortem examination on January 14 revealed enlarged tracheobronchial nodes in the area of the hilus of the right lung, which were matted together to form an encapsulated mass about 6 by 4 by 3 cm., giving the appearance of a neoplasm. The spleen weighed 400 Gm. At its lower pole there was a well demarcated mass about 8 cm. in diameter, replacing about two thirds of the parenchyma. A recurrent mass was found in the prostatic area, and all the retroperitoneal nodes were neoplastic. The histologic picture of the recurrence, as well as of the lymph nodes and the splenic metastases, was that of a diffusely growing, small cell, poorly differentiated carcinoma.

It is difficult to understand what makes the spleen so unfavorable for secondary carcinoma when its structure and function closely resemble those of lymph nodes, which are favorite sites of carcinomatous deposits. Some writers explain this by the fact that the spleen does not possess any specific parenchymatous cells; some find the reason for it in the pulsation of the organ, which would make it difficult for the tumor emboli to attach themselves; some mention the sharp angle of the splenic artery, which would keep out the metastatic emboli, and some refer to the immunologic resistance of the spleen, by which it would destroy the malignant cells if they were able to get there. That the splenic parenchyma itself is devoid of lymphatics may be still another explanation. The main reason, however, may lie in the fact that one does not look closely enough to find metastatic deposits, which at times may be minute. Until 1927, only a few cases had been described in the literature; since then, there have been an increasing number of reported cases of splenic metastasis. Krumbhaar described twenty-one metastatic carcinomas of the spleen. Yokohata, among twenty-nine unselected cases of carcinoma, was able to demonstrate metastases in ten, but they were all only of microscopic size and were situated mostly in vessels or sinuses. At this stage one can think of these collections only as emboli, the development of which into true metastatic growths is not necessarily taken for granted.

AN UNIDENTIFIED PARASITE IN THE CARDIAC MUSCLE. WILLIAM C. VON GLAHN.

A carpenter, aged 62, born in Virginia, first admitted to the hospital because of cardiac decompensation, was found to have aortic stenosis and insufficiency. At

the end of four weeks, compensation was sufficiently restored to permit his return home. He was readmitted with lobar pneumonia and died on the fourth day of his illness.

The aortic valve was extensively calcified; the heart was hypertrophied. There was consolidation of the lower and middle lobes of the right lung.

In the hypertrophied cardiac muscle the nuclei were often indented or invaginated, owing to the presence of peculiar bodies lying within the sarcoplasm. The end of the body near the nucleus was bluntly rounded; the other end was pointed. Near the bluntly rounded end was an oval vesicular nucleus containing particles of chromatin, and close to this nucleus in some instances was a solid round structure. One or more vacuoles were seen near the pointed end. The bodies measured 52.5 microns in length and 5.5 microns in width. They were usually straight, though in one instance one body was turned abruptly at right angles close to the nucleus and another was sharply bent on itself.

Two larger bodies were found which had been cut across in sectioning. One of these fragments measured 63 microns in length and 7 microns in width. Near the rounded end was a huge nucleus, 5.8 microns wide, in which were three nucleoli, the largest measuring 3.8 microns in diameter. The nucleus was constricted at its midportion as though in process of division. The other fragment, 45.5 microns long and 7 microns wide, likewise had a rounded end; its oval nucleus measured 10.5 by 4.5 microns. The single nucleolus was 2.4 microns in diameter.

Another of these bodies was divided longitudinally through part of its length so that it was roughly Y-shaped. There were two rounded ends directed toward the nucleus; the other end was sharply pointed. Close to one of the rounded ends were two nuclei; in the other was a single nucleus. In many muscle fibers fragments were found, and it was apparent that they often represented more than one of these bodies.

Staining Reactions of Bodies

Stain	Reaction
Hematoxylin-eosin	Eosinophilic
Gram	Gram-positive
Mallory's phosphotungstic acid hematoxylin	Yellow
Iron hematoxylin	Black
Carbol fuchsin followed by 1 per cent acid alcohol	Not acid-fast
Giemsa	Nucleus deep blue; remainder, robin's egg blue
Eosin; methylthionine chloride, U. S. P. (methylene blue); azure B	Nucleus very deep blue; remainder, dark blue

The only internal structure that could be distinguished in the bodies, aside from vacuoles and the nucleus with its nucleolus and chromatin material, was fine granules, usually in the blunt round portion. In the phosphotungstic acid hematoxylin preparations, the periphery of the bodies was refractive.

The bodies were not encapsulated; they seemed somewhat rigid. They were situated always adjacent to the nucleus of the muscle, and the long axis was always parallel to the direction of the myofibrils. They appeared to be surrounded by clear fluid. The myofibrils were pushed to either side by the bodies, but otherwise were unchanged. The cardiac muscle containing the bodies was not appreciably enlarged as compared to the adjacent muscle. There was no inflammatory reaction. The bodies were especially numerous in the posterior part of the left ventricle and were less frequently observed in the muscle from the apex of this ventricle. None could be found elsewhere in the heart.

The only other voluntary muscle available for histologic study was the diaphragm, and this did not contain any of the bodies.

These bodies do not conform to any known form of degeneration; their definite shape and well preserved nuclei, together with their staining reactions, indicate that they are not simple degeneration products.

They do not conform to any hitherto described parasite known to lodge in the cardiac muscle or in other muscle.

Preparations have been shown to numerous persons, including protozoologists. The consensus is that the bodies are parasitic, but none could identify them.

MYXOMA OF THE TRICUSPID VALVE. THOMAS C. JALESKI (by invitation).

An obese Negro woman, 62 years of age, was admitted to St. Luke's Hospital because of failing vision in both eyes, and was found to have bilateral cataracts. There were no other complaints, nor were there any findings indicative of heart disease. Extraction of the cataract in the right eye was performed, and on the sixth postoperative day the patient suddenly collapsed, with a clinical picture of circulatory failure, the blood pressure being 60 systolic and 40 diastolic, and the pulse very feeble. She became steadily worse and died the next day.

At autopsy the only noteworthy lesions were in the heart and the pericardial sac. There was about 100 cc. of cloudy fluid in the pericardial sac, and the pericardium was hemorrhagic. The heart weighed 325 Gm. None of the valves were thickened, and there was no evidence of endocarditis. On the anterior cusp of the tricuspid valve, situated in the middle of the valve and about 5 mm. from its free margin, was a small, spherical tumor measuring 6 mm. in diameter and projecting 4 mm. above the surface of the valve. It was attached to the valve by a short, wide pedicle. Its surface was finely nodular, and it had a translucent, gelatinous appearance.

Microscopically, the tumor was a myxoma, showing a definite pedicle and firm papilliform processes forming the major part of the growth. It had a complete endothelial covering. Stellate and spindle-shaped cells with long fibrillar processes were present in the papillae, and the presence of elastic fibers in the tumor was proved by Weigert's stain. Thionine and mucicarmine stained the tissue very faintly, possibly indicating the presence of mucin. Morphologically, the growth was therefore characteristic of true myxomas of the valve.

DISCUSSION

ALFRED PLAUT: May I rapidly show a tumor of the tricuspid valve which came into my hands two weeks ago? My associates and I performed an autopsy on a new-born infant who lived for one hour and died with signs of a disturbance in circulation. Examination gave negative results except for a large tumor arising from the tricuspid valve and obliterating the tricuspid ostium. The large distention of the right auricle is not easily demonstrable in the photograph; it was much more conspicuous in the specimen. The tumor has a broad base. In the photograph one can see the tricuspid ring, the normal musculature of the myocardium and the tumor, which I rightly or wrongly call an angiofibroma.

Another picture shows connective tissue in the tumor and a distinct endothelial lining. The same picture in another area shows peculiar large clear cells which I do not recognize. The unusual thing about this tumor is its size. It led to obstruction of the flow of blood at the tricuspid ostium, and I think that that caused death. Otherwise the child was normal; there was nothing in the skull to account for death directly after birth.

FOUR CASES OF THYMIC TUMORS (TWO WITH DISTANT METASTASES). ANGELO M. SALA and ELMA BARANY.

We have been fortunate in having an opportunity within a short time to study four tumors of the thymic region; three patients have come to autopsy, and the fourth is still under observation. The uncommon occurrence of these tumors may be judged from the fact that in a rich experience including nearly

seventeen thousand autopsies, Douglas Symmers was able to collect only twenty-five cases (*Ann. Surg.* **95**:544, 1932).

CASE 1.—A white man, 53 years of age, was admitted to the hospital on Feb. 17, 1933. The previous November he noticed a change in his voice which he attributed to a cold. He was better in two weeks, but relapsed after a month, at which time a roentgenogram of the chest revealed the true state of affairs. Besides the condition in the chest, there was a hard, fixed mass in the left supraclavicular region, just behind the lower third of the sternocleidomastoid muscle. Biopsy on this mass showed a reticulum cell lymphosarcoma. At autopsy, on March 11, 1933, a tumor measuring 15 by 6 by 5 cm. was found in the region of the thymus; it extended upward to just below the thyroid cartilage and downward to below the origin of the great vessels, invading the pericardium. A nodule 3 by 1 cm. was found in the right auricle, apparently invading the cardiac muscle by extension of the original tumor through the pericardium. Two other small nodules were found in the substance of the left ventricle, and there were metastatic foci in the right kidney and spleen, as well as in the neck, as previously noted. The roots of the lungs were adherent to the tumor, but the lungs were not invaded.

CASE 2.—This case is presented through the courtesy of Dr. Douglas Symmers, who performed the autopsy a short time ago. A white man about three months before death began to complain of fulness in his head on bending over. One month later there was noticed a small lump in the left sternoclavicular region which caused discomfort on breathing. The lump was removed for biopsy, and the discomfort disappeared. Two weeks before this operation there was noted a slight, intermittent paresthesia of the areas of the right and left ulnar nerves. There was no cough, loss of weight or dysphagia. At autopsy there was found a tumor measuring 15 by 10 by 5 cm., occupying the entire anterior mediastinum. It was attached to the pericardium on the right side. It pushed aside and compressed the upper lobe of the right lung but was not adherent to it. On the left side it was adherent to the lung but did not infiltrate. The tumor as a whole appeared to be well encapsulated and did not invade the surrounding structures. Many of the nodes immediately adjacent to the neoplasm were enlarged and rather firm.

Histologically, the two tumors described were identical, both in hematoxylin and eosin and in silver preparations. They were both definite reticulum cell lymphosarcomas.

CASE 3.—A white man, aged 45, was admitted to the hospital on March 23, 1933. The chief complaints were cough, weakness and loss of weight of three months' duration. Six weeks before admission a mass in the left axilla was noted. Two weeks before admission hoarseness developed. Death occurred in a few weeks as a result of lobular pneumonia. At autopsy there was found in the region of the thymus a tumor measuring 6 by 3 by 2 cm., extending down on the pericardium, but not penetrating it. The nearby hilar nodes were markedly enlarged. There was also enlargement of the retroperitoneal and peripancreatic nodes, as well as metastatic deposits in both suprarenal glands. The histologic picture of the primary tumor and of the metastases was that of epithelioma. There were noted in many areas of the original tumor, as well as in the axillary mass, condensations of the epithelium suggesting definite attempts at the formation of Hassall's corpuscles.

CASE 4.—A 28 year old white woman was admitted to the hospital, on Feb. 9, 1933, complaining of intermittent paroxysmal attacks of cough for one year, with expectoration of whitish, occasionally thick phlegm which was never streaked with blood. For two months she had had generalized pruritus. There was enlargement of the lower cervical nodes on the left side, and a large, firm node was present in the right axilla. Roentgenograms of the chest showed a large mass in the midline in the region of the thymus. A biopsy specimen from one of the cervical nodes showed the typical picture of Hodgkin's disease. This case

is therefore presented as one of thymic Hodgkin's disease. The patient is still under observation and is receiving high voltage roentgen treatments.

DISCUSSION

NATHAN CHANDLER FOOT: The third case is of particular interest on account of its rather unusual features. I have had the good luck to collect about five of these malignant tumors of the thymus in the course of a number of years, and I find that they fall into three groups: The lymphoid group includes a reticuloendothelial type and an indeterminate Hodgkin-like type. The epithelial group is characterized by the production of large pearl-like bodies which resemble and probably represent a part of Hassall's corpuscles. The third group combines the characteristics of the other two and shows a great many epithelial ducts such as were seen in the third case reported by Dr. Sala and Dr. Barany. I have been on the lookout for another case. These tumors are somewhat difficult to classify; in the case which I saw, the growth developed in a young child and had somewhat teratoid characteristics; part of it was lymphoid, and part of it was made up of epithelial ducts without marked production of Hassall's corpuscles.

I do not think that distant metastases are as common as Dr. Sala indicates. Most of these cases show a predominant tendency toward local extension and invade the glands about the pulmonary hilus and the pericardium without going much farther, working their way into the lung and not going outside. The cases reported here present an unusually high number of distant metastases. In one of my cases there was a very distant metastasis. The tumor was a lymphosarcoma of the thymus; the patient had all the symptoms of acute lymphoid leukemia with a typical blood picture, and the whole blood stream was flooded with these cells although no other productive foci were found except the lymphosarcoma of the thymus.

ANGELO M. SALA: There is no denying the difficulties of a histologic classification of these thymic tumors, and yet I feel that a classification ought to be attempted because it is possible in practically all cases. The term thymoma should be dropped as both evasive and meaningless.

The leukemic conversion spoken of by Dr. Foot occurs only in the lymphosarcoma group. Symmers described three such cases in his report; I have observed one. There is a question in these cases whether one is not dealing from the beginning with a leukemia, of which the thymic enlargement is a manifestation.

Dr. Foot is right when he says that distant metastases from these tumors are not as common as this small series would lead one to believe. It is a chance occurrence that of our three cases in which autopsy was performed, two showed distant metastases.

CYSTIC DEGENERATION OF THE POSTERIOR LOBE OF THE PITUITARY GLAND. DOMINIC A. DE SANTO (by invitation).

Cystic degeneration of the posterior lobe of the pituitary gland was encountered in a Russian Jew, 32 years old, who weighed approximately 450 pounds (200 Kg.) and gave a history of increasing obesity since the age of 20, voracious appetite, pathologic somnolence resembling true narcolepsy, severe frontal headache and polyuria. Clinically, the patient showed exophthalmos, hypertension, genital atrophy, generalized obesity, accentuated over the abdomen and thighs, a narcolepsy-like syndrome consisting in prompt onset of sleep almost immediately after sitting down, a diminished, instead of an increased, tolerance for carbohydrate, and a basal metabolic rate within normal limits.

At autopsy, death appeared to have been caused by hypertensive heart disease in congestive failure. The diencephalic area showed no gross alterations and unfortunately was not preserved for study. The sella turcica appeared normal; the pituitary gland was of normal size, but the posterior lobe appeared bulbous and on sagittal section showed a gross cystlike alteration. The cyst contained shreds of granular débris.

On serial section, approximately three fourths of the posterior hypophysis appeared destroyed. An irregular cavity was found without a lining and without significant alterations in the small surrounding rim of tissue. Diagnoses of gumma, tubercle, necrotic tumor, embolus, ischemic softening and retention cyst of the pars intermedia were considered and excluded. An area in the anterior lobe showed a localized overgrowth of fibrous tissue with focal disintegration of a few acini. The anterior lobe was otherwise normal.

The thyroid gland showed slight colloid transformation. The testes showed striking changes consisting of a diminution in the size and number of the tubules and in the number of interstitial cells.

Whatever the cause of the lesion, it was considered to be chronic, and to it was assigned responsibility for the symptoms.

It is recognized, however, that in the absence of diencephalic studies, the whole picture could be equally well ascribed to some unnoticed lesion of the tuberal region, especially since the patient had suffered previously from attacks of grip. From this point of view the syndrome would probably be postencephalitic.

DISCUSSION

ALFRED PLAUT: Dr. De Santo mentioned our work published eleven years ago. This study was begun by Simmonds, the man for whom hypophyseal cachexia is named. I repeated his work in thirty-five autopsies on patients with pyemia, and metastatic lesions were found in the hypophysis in seventeen cases. All these, however, were cases of true pyemia. I should not venture to say that from this high percentage one could draw any conclusion as to a possible relation between disturbances of internal secretion and preceding ordinary infections of the throat. Tonsillitis and true staphylococcic pyemia are widely differing diseases. It seems rather difficult to me to obtain a reliable statistical basis for establishing a connection between the frequent infections of the throat and the occurrence of disturbances in internal secretion.

The case reported by Dr. De Santo is unusual, and it is difficult to say anything about it. It would be necessary to know more details about the lesion in the posterior lobe, for instance, whether there was necrosis, neuroglial overgrowth or epithelial structures pointing to a cyst. Why are the changes which the patient exhibited ascribed to a disturbance in the posterior lobe of the hypophysis? The patient's symptoms certainly were not those which one is accustomed to see in disease of the posterior lobe. Were there any changes in the blood vessels supplying the hypophysis? Since the original title of the paper mentioned ischemic change, I have brought lantern slides illustrating two instances of true ischemic changes in the hypophysis. Such lesions are rare and are often overlooked because the hypophysis is not examined.

The first case was that of a boy 11 years old who died soon after the onset of the basal streptococcic meningitis which had its origin in the sphenoid sinus. Even with the naked eye one could see the extensive central necrosis in the anterior lobe of the hypophysis. There was no inflammation in the peripheral layers of the anterior lobe. Obviously the thick, purulent exudate had blocked the tissue spaces and the lumens of the vessels in the surroundings of the hypophysis, thus leading to a true ischemic necrosis.

The second instance of necrosis in the anterior lobe was in a man 82 years old. The slide shows the very narrow lumen of one hypophyseal artery. One is not astonished, therefore, to see the necrosis in the anterior lobe.

If at autopsy the hypophysis received the attention that one is accustomed to give to the suprarenal glands or to the spleen, such lesions probably would be found more frequently.

SOLOMON SILVER: My attention was primarily attracted by the idea of ischemic degeneration of the posterior lobe of the pituitary gland, but apparently Dr. De Santo did not present the case as one of this condition. I find this particularly interesting because, so far as I know, ischemic degeneration occurs

only in the anterior lobe. Apparently, as was pointed out twenty years ago by Simmonds, the arteries of the anterior lobe are functionally end-arteries, whereas the arteries in the posterior lobe anastomose with each other, and although embolism of the posterior lobe may be more common, subsequent changes, especially with regard to infarction, are rare; in most of the cases I was able to collect in a rather extensive survey of the literature, the pathologic changes in the posterior lobe were scanty compared to those in the anterior lobe.

Considering Dr. De Santo's case clinically, it is unfortunate that the diencephalic areas were not investigated. It is hard to believe, in view of all the recent work on the nature and the cause of polyuria and polydipsia, that the posterior lobe is involved. One must accept the fact that the posterior lobe can be completely removed without giving any of these symptoms, and that in the absence of the posterior lobe, properly placed diencephalic punctures can give rise to all of the symptoms. It seems to me that the clinical picture was diencephalic. This cannot be proved in the absence of the tissue, but changes in the posterior lobe even more extensive than those shown seldom give rise to this picture unless the tumor has spread to the diencephalic areas. I should tend to believe that the whole syndrome was diencephalic, probably on the basis of a "missed" encephalitis.

ALFRED PLAUT: Ischemic lesions are much more frequent in the anterior lobe, but they occur in the posterior lobe also.

DOMINIC DE SANTO: In regard to the title of this presentation, in studying serial sections I encountered certain changes in the vessels and slight thickening of the intima and of the elastic tissue which on reconsideration I thought were the normal concomitant of the hypertension. It occurred to me then that this condition might have been ischemic atrophy; but I said at the outset that I withdrew that suggestion, because it would be difficult to maintain the premise that there was ischemic degeneration. I do not know the nature of the condition.

As to the histologic appearance of the surrounding rim of tissue, there was no evidence, so far as I could see, of glial overgrowth, nor was there any deviation from the normal appearance of the pituitary gland that shed any light as to what the condition was. There was no endothelial lining. In serial sections the cyst did not communicate with the colloid cysts of the pars intermedia, so that it undoubtedly was not a retention cyst of the pars intermedia, such as might conceivably develop.

As to whether the symptoms were due to this lesion, that is difficult to state. I considered the possibility of the condition being postencephalitic, particularly since the patient had had several attacks of what apparently was grip. On the other hand, nothing like this has been reported in encephalitis, and one cannot ignore the lesion.

As to whether all of these symptoms were due exclusively to tuberal lesions, I do not know that that has been definitely proved. It seems to be the belief of Cushing and others that the pituitary gland and the hypothalamus form a system, and that a modified so-called hypopituitary syndrome may result from lesions anywhere in this pituitary-mesencephalic system. I do not agree that it is entirely established that the posterior lobe of the pituitary gland cannot give rise to deficiency symptoms of the type described, even though tuberal extirpation may result experimentally in hypogenitalism, obesity and high carbohydrate tolerance, polyuria and other conditions, and even though the original hypophysectomies have been criticized, because it has been maintained that in removing the pituitary gland the tuber has been accidentally injured. In further experiments Cushing showed that these so-called tuberal symptoms have developed when merely the hypophyses was destroyed. In other words, if all the symptoms are due to the tuber cinereum, the pituitary gland has practically no function. I think that the lesion must have some bearing on the development of the symptoms, but I have no way of proving it.

MYOBLASTOMA OF STRIATED MUSCLE. PAUL KLEMPERER.

Neoplasms composed of myoblasts, the ancestral cells of striated muscle, were first described by Abrikossoff in 1926. There is now a total of about fifty recorded observations, if one includes those which are casually mentioned in discussions occasioned by the report of such cases. This indicates that this variety of tumor is certainly not uncommon. Because there are only two reported cases in the American and English literature, and these were recorded under the term of "rhabdomyoma of the tongue" (Keynes, Dewey), a report is here made of six additional observations collected in the last four years. The histologic appearance of these tumors is uniform. They are composed of large round or polyhedral cells and ribbon-like syncytial masses which are surrounded by slender collagen fibers. The most characteristic feature, however, is the pronounced granular structure of the cytoplasm.

In the differential diagnosis the xanthomas must be chiefly considered, a fact which has been stressed by several writers. In fact, this mistake in diagnosis has occasionally occurred (Peyron). However, the absence of fat in frozen sections rules out xanthoma, although the cells in paraffin sections resemble those of xanthoma.

The tumors that I have observed were localized in the skin (three cases), the tongue, the vocal cords and the gastrocnemius muscle, respectively. A survey of all the cases reported shows the following distribution: tongue, twenty-one cases; maxilla (congenital epulis), four; skin, four; vocal cords, three; mandible, two; breast, two; lip, one, and upper part of the esophagus, one.

This summary reveals a conspicuous preference for the upper digestive and respiratory tract, with the tongue as the most frequent site of localization.

As to malignancy, there was no recurrence in any of the cases here reported from six months to three years after excision. Only one case in the literature (Meyenburg) was malignant as evidenced by repeated recurrence with local invasion after operation.

The myoblastomas of striated muscle represent a well defined oncologic group of practical importance.

DISCUSSION

NATHAN CHANDLER FOOT: Just this afternoon I was puzzling over a tumor which was identical with those which Dr. Klemperer has shown. It was taken from a Negress, 74 years of age. It had been present for a number of years and had been treated in various ways. It was finally removed by a surgeon with the tentative diagnosis of carcinoma. It showed little epithelial proliferation, as Dr. Klemperer mentioned, but showed the peculiar infiltrating growth of these granular cells. I was thinking of making a diagnosis of xanthoma, although I was waiting until tomorrow for another look at the tumor. Dr. Klemperer has made the diagnosis easy.

Book Reviews

Arteriosclerosis: A Survey of the Problem. A publication of the Josiah Macy, Jr., Foundation. Edited by Edmund V. Cowdry, Washington University, St. Louis. Price, $5. Pp. 617, with 88 figures. New York: The Macmillan Company, 1933.

This book presents the results of an earnest cooperative attempt to promote the investigation of arteriosclerosis by a survey that would indicate promising lines of approach. It contains twenty-one articles on various aspects of arteriosclerosis by well qualified writers, many of whom are widely known from their previous work in this field. In the foreword and preface Ludwig Kast, the director of the Josiah Macy, Jr., foundation, and Edmund V. Cowdry, the editor, explain fully the considerations that have guided them in the preparation of the book. Dr. Kast expresses the hope that the survey will be accepted by investigators, clinical as well as experimental, as an invitation for suggestions "as to how to move closer through joined efforts to an understanding of 'arteriopathy.'" And Dr. Cowdry trusts that the book will be helpful to investigators, physicians and students of medicine. In the introduction Ludwig Aschoff discusses the essential nature of arteriosclerosis with a view to defining the process as clearly and as closely as possible. "To sum up, we understand by arteriosclerosis a chronic disturbance of the vessels which manifests itself by deposits of the most varied kinds in the vascular walls and which becomes irreversible on reaching its climax in vessels impaired by changes attending the process of aging with resulting deformation of the lumen and brittleness of the vascular walls." Aschoff regards changes in the ground substance as of great importance in the development of arteriosclerosis. Esmond Long writes an interesting and lucid historical review of the development of knowledge of arteriosclerosis, with emphasis on the recent views of its etiology. Then follow chapters on the structure and physiology of blood vessels (E. V. Cowdry), the physical properties of arteries in health and in disease (Crighton Bramwell) and the mineral constituents of blood vessels as determined by incineration (A. Policard). Policard writes: "The importance of the techniques outlined in this chapter is that they permit the investigator to determine accurately the very earliest changes in mineral constituents in beginning arteriosclerosis. It is these earliest lesions which, when examined from every angle, may be expected to afford clews to the etiology of the condition. As I have already stated, work along this line has a definite bearing upon physical changes in the elastic fibers and upon the interesting theory of Wells on the aging of colloids. It should be followed." The statistical aspect of arteriosclerosis is discussed by Edgar Sydenstricker; the relation of arteriosclerosis in lower mammals and birds to the human disease is presented by Herbert Fox (good figures); the rôle of climate and race is the topic of the chapter by Percy Stocks, and nutrition in relation to arteriosclerosis is considered by Soma Weiss and George R. Minot. William Ophüls, who died recently, writes on the pathogenesis. N. Anitschkow concludes his chapter on experimental arteriosclerosis (illustrated) as follows: "Feeding with cholesterin is the only method which makes it possible for us to produce in certain species of animals changes that may be regarded as equivalent to those typical of human atherosclerosis. The experimental investigations based on this method, which will be supplemented by further experiments, have opened the way to a systematic analysis of the pathogenesis and etiology of the disease. Undoubtedly the results thus obtained will also provide valuable indications in respect to prophylactic and therapeutic measures." In his important discussion of the chemistry of arteriosclerosis, H. Gideon Wells supports the view that it "depends primarily on changes in the elastic tissue that reduce its resiliency and lead to arterial dilatation"; the change in the elastic fibers in arteries "is only that always produced sooner or later

as the natural fate of all elastic colloidal gels"; intimal thickening, lipoid deposits and calcareous deposits are secondary processes. After reviewing the rôle of infections, William G. MacCallum finds "but little evidence in favor of the idea that infections, whether acute and chronic, play a great part in the pathogenesis of arteriosclerosis." Then come instructive chapters on regional arteriosclerosis: retina (J. S. Friedenwald), brain and cord (Stanley Cobb and Daniel Blain), coronary (good illustrations) and pulmonary arteries (Howard T. Karsner, two chapters) and abdominal viscera and extremities (E. T. Bell). The relation of hypertension to arteriosclerosis is analyzed by Fritz Lange, who holds that hypertension is a symptom the cause of which remains to be found. (In this chapter the German term "hypertonia" is used in place of hypertension, without any apparent justifiable reason.) George Dee Williams contributes a chapter on the hereditary aspects of arterial hypertension. John Wyckoff concludes his chapter on the treatment of arteriosclerosis with the statement that "to institute rational treatment much more searching investigation is required." At the end of each of these chapters is a list of select references. In the final chapter Alfred E. Cohn writes a constructive and judicious summary of the views and suggestions of his fellow contributors. This summary merits close and careful study. There are good subject and author indexes. A lighter and duller paper might have been used. The book weighs nearly 4 pounds. The articles reflect the individual views of the authors. To discuss in detail these views, often simply and directly expressed, is out of the question. No formal agreements are recorded either as to pressing problems or as to investigative approach. But there is the significant, even if tacit, acceptance of the powerful integrative principle that arteriosclerosis, no matter how defined, is the result of factors involving the organism as a whole. The hopes of the sponsors of the book that it may advance the understanding of arteriosclerosis are justified.

Urine and Urinalysis. By Louis Gershenfeld, Ph.M., B.Sc., Ph.D., Professor of Bacteriology and Hygiene and Director of the Bacteriological and Clinical Chemistry Laboratories at the Philadelphia College of Pharmacy and Science. Price, $2.75, net. Pp. 272, with 36 engravings. Philadelphia: Lea & Febiger, 1933.

The first part of this book deals briefly and in elementary fashion with the structure and function of the kidneys; with urine, its physical characteristics and chemical composition, and with the abnormal constituents of urine. The second part deals with urinalysis, with chapters on qualitative tests, quantitative estimations and microscopic examination of urine. In the third part special urinary tests are described. There is an appendix on special apparatus and on reagents. The introduction contains a condensed review of the history of urinalysis. The illustrations represent for the most part apparatus, some of which, e. g., the hand centrifuge (fig. 15), seems rather antiquated. The presentation is concise and orderly. The various methods of analysis are described clearly. The book may be recommended as a reliable guide in the technic of urinalysis. No attempt is made to interpret results. Its sole object is to guide the analyst to secure accurate data for clinical use.

A Text-Book of Neuropathology. By Arthur Weil, M.D., Associate Professor of Neuropathology, Northwestern University Medical School, Chicago. Cloth. Price, $5. Pp. 335, with 260 engravings. Philadelphia: Lea & Febiger, 1933.

The object of this book is "to give a review of the present stage of our knowledge of neuropathology," which "is the study of the nervous tissue in disease and the determination of deviations of its structure from the normal." The book deals principally with the microscopic study of these changes. The chapter headings give a good idea of its scope: changes produced by autolysis and fixation, diseases of the ganglion cells, the glia and its pathology, pathology of the myelin sheaths and the axis cylinder, anemic softening, arteriosclerosis,

inflammation, infections, intoxications, injuries, degenerative diseases, tumors, congenital malformations, appendix. In the appendix are tables of the weight of the brain, directions for the postmortem examination and fixation of the central nervous system and descriptions of staining methods. At the end is a list of references to important recent work in neuropathology arranged according to the order of the chapters in the text. For ready reference this does not seem to be a good arrangement. In general, the descriptions of the microscopic appearances of the nerve tissues in disease are accurate and clear. The illustrations, mostly original, are excellent. The book will be of much help to students of neuropathologic histology. In fact, it is so predominatingly histologic in scope that it hardly deserves the title of "A Text-Book of Neuropathology." To merit this title fully extensive expansion is required. This may be possible in a new edition. If the call comes for a new and revised issue, certain matters and questions should receive special attention. Does the frequent use of German words help the presentation? The following German words are now used: Wasserfehler, aequivalent Bild, homogenisierende Zellenerkrankung, Stäbchenzellen, Glia-rasen, gemästete, Wetterwinkel, flohstich Encephalitis, Lückenfelder, Anfälligkeit and Aufbrauch. Certainly the meaning of most of these words can be conveyed adequately by simple English terms. In an eventual expansion of the book thorough attention should be given to the systematic description of gross appearances. At present, for instance, nothing is said about the gross characteristics of the brain in acute poisoning with carbon monoxide and of different tumors of the brain. The highly important subject of meningeal hemorrhage merits systematic treatment in a neuropathologic discussion. The section on Blastomyces infection (p. 172) needs revision in any case. What is Sporotrichon? Should not "functional psychoses," epilepsy and senile dementia be mentioned? Is not herpes zoster, which is not mentioned, a disease of the nerve tissue? Should not the cerebrospinal fluid be discussed in detail? Is the use of the word toxin as synonymous with poisons or morbific substances of any kind or nature justifiable? Are not the phrases commonly used about toxins in this general sense and their effects on cellular structure just cloaks of ignorance of misleading verisimilitude? What is known about the toxins of the spirochete of syphilis? If it is decided to limit further editions of the book to neuropathologic histology, the field it now covers satisfactorily, such limitation should be indicated by a change in the title.

The History and Epidemiology of Syphilis. The Gehrmann Lectures, University of Illinois, 1933. By William Allen Pusey, A.M., M.D., LL.D., Emeritus, Professor of Dermatology, University of Illinois, Sometime President of the American Dermatological Association and of the American Medical Association. Price, $2. Pp. 105. Springfield, Ill.: Charles C. Thomas, 1933.

These three lectures are an elaboration of parts of the author's monograph on "Syphilis as a Modern Problem," published in 1915. The history, epidemiology and control of syphilis are reviewed in the light of the knowledge and experience of today. The first lecture describes graphically the startling appearance in southern Europe at the end of the fifteenth century of a new disease, somewhat later called syphilis, which spread rapidly in all directions. The record is unique —there is no record of any other great disease that has established itself with such precision and rapidity. In view of the lack of any indications of the presence of syphilis earlier in Europe (and Egypt) and in view of the evidence unearthed by Montejo y Robledo that syphilis was brought to Spain by the sailors of Columbus, as well as other considerations, the author concludes that "the preponderance of evidence for the American origin of syphilis is overwhelming." In the second lecture the growth of the knowledge of syphilis from the earliest descriptions of its manifestations in 1496 down to today is detailed clearly and instructively. This growth coincides with the growth of medicine in general.

The disastrous effect of John Hunter's experiment on himself and the gradual groping back into the right road are admirably sketched. Copies of old illustrations, some of them among the earliest dealing with syphilis, and many portraits of the great students and investigators of syphilis add to the interest of these two lectures. The third lecture is devoted to a discussion of the spread or epidemiology of syphilis under four headings: the reservoir of infection, the infecting organism, the susceptible host and the means of transmission. The conclusion is that syphilis can be controlled if handled as a sanitary problem. "We should strive to make it as far as possible such a problem." The book should be read widely by persons who have a special interest in syphilis. It has educational value in a large sense because it tells so well how syphilis has come to be understood as fully as it is and how thoroughly the ground for its control has been prepared.

Surgical Pathology. By William Boyd, M.D., M.R.C.P., F.R.C.P., Professor of Pathology, University of Manitoba. Third edition. Cloth. Price, $10. Pp. 866, with 490 illustrations. Philadelphia: W. B. Saunders Company, 1933.

The first edition of this book was published in 1925 and was well received. The second edition was published in 1929. The appearance of the third edition indicates its continued usefulness and popularity. Considerable appropriate new material has been introduced, and many of the sections have been revised or rewritten, but the size of the volume has not been increased. The book has been brought well up to date and may be recommended as a well written and useful handbook in its field.

Books Received

THE GREAT DOCTORS: A BIOGRAPHICAL HISTORY OF MEDICINE. Dr. Henry E. Sigerist, Professor of the History of Medicine, Johns Hopkins University. Translated by Eden and Cedar Paul. Price, $4. Pp. 436, with over 60 illustrations. New York: W. W. Norton & Company, Inc., 1933.

BACTERIAL INFECTION, WITH SPECIAL REFERENCE TO DENTAL PRACTICE. J. L. T. Appleton, Jr., B.S., D.D.S., Professor of Microbiology and Bacteriopathology, the Thomas W. Evans Museum and Dental Institute, School of Dentistry, University of Pennsylvania. Second edition. Price, $7, cloth. Pp. 654, with 122 engravings and 4 colored plates. Philadelphia: Lea & Febiger, 1933.

FOOD, NUTRITION AND HEALTH. E. V. McCollum, Ph.D., ScD., and J. Ernestine Becker, M.A., Professor and Associate of Biochemistry, School of Hygiene and Public Health, Johns Hopkins University. Third edition. Price, $1.50, postpaid. Pp. 146. Baltimore: E. V. McCollum and J. Ernestine Becker, 1933.

COLOUR VISION REQUIREMENTS IN THE ROYAL NAVY: XII. REPORTS OF THE COMMITTEE UPON THE PHYSIOLOGY OF VISION. Medical Research Council, Special Report Series, No. 185. Price, 1s. Pp. 58. London: His Majesty's Stationery Office, 1933.

LES TROUBLES DE L'ÉLIMINATION URINAIRE DE L'EAU: ETUDE PHYSIOPATHOLOGIQUE ET CLINIQUE. Jules Cottet, Ancien interne des hôpitaux de Paris. Price, 32 francs. Pp. 212. Paris: Masson et Cie, 1933.